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**ABSTRACTS OF
COMMUNICATIONS**

ADRIAN, E. D. (Cambridge). **The activity of the mammalian olfactory apparatus.**

The electrical responses accompanying olfactory activity have been investigated in rabbits, cats, and dogs. A fine wire electrode can be thrust into the olfactory bulb through an opening in the floor of the frontal sinus and the olfactory tract can be reached through the wall of the orbit. The results agree in general with those already found in the hedgehog. The current of air through the nose at each inspiration produces a series of large potential oscillations throughout the bulb and a discharge of impulses from the mitral cells. If the inspired air has been exposed to clove oil, valerian, aniseed, &c., the discharge of impulses is greatly increased. The potential waves may increase in number, or may break down into small rapid oscillations, the result depending on the nature and depth of the anaesthetic. Mechanical stimulation of the olfactory epithelium is effective and smoke blown into the nose causes an intense discharge. The response to an air current seems to depend in part on mechanical stimulation of the olfactory cells. The reactions of the olfactory pathway show many points of resemblance with those of the retina or the receiving areas of the cortex, but it has not yet been possible to decide whether different smells produce different spatial patterns of activity.

BACHRACH, E. (Paris). **Propriété thermo-régulatrice des cations alcalins et alcalino-terreux (physiologie et pathologie).**

Physiologie: Nos expériences (1941) ont montré une relation étroite entre la température des organismes et la composition chimique du milieu baignant leurs cellules.

Les sels minéraux montrent une propriété nouvelle: ils sont à la base de la fonction thermo-régulatrice. Ce sont les principaux facteurs biothermiques. Le cation joue le rôle actif.

Nous distinguons deux groupes: les alcalins — sodium et potassium — le potassium surtout — permettent l'élévation de la température ou augmentent la résistance aux températures élevées; les

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alcalino-terreux — calcium et magnésium, surtout le magnésium — permettent d'abaisser la température ou diminuer la résistance aux températures élevées. *La température des vertébrés est fonction: du Δ (sels et sucres), de la nature des cations, de leur quantité respective et du rapport de celles-ci.*

Les caractéristiques biothermiques d'une fonction déterminée ne sont pas stables, mais *contingentes*, sous l'influence de la composition du milieu en électrolytes. Suivant l'organe et la fonction envisagée, la position du point biothermique et la marge du fonctionnement varient. Chaque cation paraît imposer un point biothermique qui lui est propre. Exemple: *Fonctionnement automatique du ventricule isolé d'Hélix*. L'optimum thermique pour la fréquence des contractions est fixé à 36° en milieu équilibré de $\Delta = 0.55$, à 31°5 en milieu NaCl, à 29° en milieu CaCl₂, à 22° en milieu MgCl₂, isotoniques au milieu équilibré.

La température limite inférieure du fonctionnement automatique va de -2° (Centigrade) en milieu NaCl $\Delta = 0.55$ à +44° en milieu

isotonique $\frac{\text{NaCl}}{\text{KCl}} = 6$; soit un déplacement d'une caractéristique biothermique de 46°. Les températures optima et limite supérieure du même fonctionnement peuvent être déplacées de 20°.

En milieu NaCl l'optimum thermique du fonctionnement automatique est à 31°5 (fonctionnement hétérotherme); en milieu

$\frac{\text{NaCl}}{\text{KCl}} = 14$ à 37°4 (fonctionnement mammifère), en milieu

$\frac{\text{NaCl}}{\text{KCl}} = 7$ à 41° (fonctionnement oiseau).

Pathologie: La fièvre résulterait d'un déséquilibre cationique du sérum. Il y a accumulation plus ou moins marquée des cations Na⁺ (parfois K⁺), et simultanément appauvrissement des urines en sels, surtout en Na⁺.

Hypothèse: Sous l'influence de substances étrangères ou de toxines, le fonctionnement rénal est modifié pour les sels, surtout pour Na⁺.

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BAZETT, H. C. (Philadelphia, Pa.). **Temperatures in the arteries and veins in man.**

The data reported were obtained by groups at the University of Pennsylvania and Climatic Research Laboratory. They indicate pre-cooling of arterial blood in transit to the periphery, owing to heat exchange with cooled blood returning in venae comites. Temperatures have been measured by thermocouples built into hypodermic needles (diameter 0.4 mm.) or by plastic covered wires of the same diameter introduced through a slightly larger needle. The latter can be passed along the vessel to distances of several centimeters and be left in place for hours.

At a room temperature of 22° brachial temperatures ranged from 36.3° to 37.1° and radial from 35.5° to 36.5°. In a cold environment (4° to 18°) the temperatures ranged, brachial 31.1° to 36.1° and radial 21.5° to 33.0°. In cold or neutral conditions temperatures in superficial veins were lower in peripheral than in more central localities. In a warm room the more peripheral veins might have the higher temperatures.

When arterial temperatures were low, a rapid rise was obtained when the return of cooled venous blood was impaired by light compression.

The data are interpreted as indicating mechanisms for regulating heat exchange. Precooling of arterial blood implies rewarming of venous blood by an internal exchange of heat, which economizes loss of heat to the environment. In warmth this effect is minimized and venous blood is allowed to lose more heat during its return when diverted to a superficial course.

Data are presented to indicate that an actual saving in heat exchange is attained by these reactions. Paradoxical changes which have been observed in skin temperatures also readily become explicable. Changes in blood temperatures are great and cannot be neglected in considering gas exchange, nor are the variations caused in blood viscosity negligible. The possible direct effects of large changes in temperature in the blood deserve more consideration.

BEYER, K. H., SPRAGUE, J. M., and VERWEY, W. F. (Glenolden, Pa.). The selective inhibition of the renal tubular excretory mechanism for penicillin.

The renal elimination of penicillin is by tubular excretion as well as by glomerular filtration. These combine to account in large measure for the wasteful physiological economy of the agent. Research dealing with the inhibition of the renal tubular excretion of penicillin has led to the synthesis of a new compound for this purpose and to a concept of its mode of action.

The compound is 4'-carboxy-phenylmethanesulfonamide, for which we have proposed the name caronamide.

It appears that the effect of caronamide is to inhibit selectively and reversibly a definitive component of the transport mechanism for the renal tubular excretion of penicillin and certain other compounds. This hypothesis is substantiated by the following findings: (1) The coadministration of caronamide depresses the renal clearance of penicillin to or slightly below glomerular filtration rate. (2) The compound inhibits the tubular excretion of penicillins F, G, K, and X, as well as that of para-aminohippurate. (3) The extent and duration of this effect are dependent on the plasma concentration and rate of elimination of caronamide. (4) The rate of elimination of the caronamide itself is equivalent to the glomerular filtration, ammonia synthesis, or any other renal transport mechanism studied, such as those for glucose, amino acids, urea, and sulfonamides. (6) It does not influence materially systemic blood pressure and kidney volume at effective plasma concentrations. (7) Caronamide has a relatively low order of systemic toxicity, and (8) is rapidly absorbed when administered orally.

Certain of these characteristics serve to distinguish the action of this agent from two mechanisms previously described whereby one compound could inhibit selectively the tubular excretion of another. These are: (1) The tubular excretion of one compound may be suppressed by the simultaneous excretion of another agent by the same transport mechanism, such as the 'mass action' inhibition of diodrast excretion by phenol red, and the inhibition of penicillin excretion by *p*-aminohippurate. (2) Inhibition may result because the

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effect of the agent is on a process that is essential to the integrity of the tubular epithelium and the body as a whole; such a process explains the glycosuria following the inhibition of glucose phosphorylation by phlorhizin.

The competitive inhibition of the renal tubular excretion of penicillin by caronamide may be likened to the *in vitro* competitive inhibition of the succinoxidase system by malonate.

HENNY, GEORGE C. (Philadelphia, Pa.). **Electrokymograph: apparatus for recording cardiovascular phenomena utilizing the roentgenoscope.**

The elektrokymograph is an electrical apparatus which records on bromide paper variations in light intensity. Any physiological process which may be made to vary the intensity of light falling on the photo-sensitive surface of the pickup tube may be recorded.

For recording motions of the cardiac border a standard medical fluoroscope is employed. The X-ray shadow of that portion of the cardiac silhouette to be investigated is limited by a lead diaphragm 5 mm. by 20 mm. The X-rays after passing through the patient and the diaphragm aperture fall on a small piece of fluorescent screen in the pickup device. The cardiac shadow moves across the rectangular aperture, covering more of it in the diastolic phase and less of it in the systolic phase of the cardiac cycle. The X-ray shadow, moving on the small piece of fluorescent screen behind the diaphragm, produces a variation in intensity of the fluorescent light. The fluorescent light illuminates the photo-sensitive surface of the photo-electric tube and is there converted into a varying electric current which is closely related to the motion of the cardiac border. The electric current is recorded by the string galvanometer of a standard electrocardiograph on 6 cm. paper which moves ordinarily at 25 mm. per second. The usual timing lines are also recorded. The electrical output of the multiplier phototube is sufficient to operate, without further amplification, the string of the galvanometer. The resulting records show surprising detail of the cardiac-shadow motion.

By simultaneously recording the carotid pulse on the same strip of bromide paper as the elektrokymogram, interpretation of the

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heart border motion is greatly facilitated. Furthermore, a coordinating time axis is obtained so that electrokymograms of various points of the cardiac and great vessel shadows made during one examination may be closely aligned in respect to time.

The apparatus will be described in detail and the features of the electrical circuit requiring special attention will be emphasized.

BOONE, BERT R. (Philadelphia, Pa.). *Application of the electrokymograph to the study of cardiovascular physiology.*

The electrokymograph, used with the fluoroscope, provides an apparatus specifically designed for the convenient recording of heart border and great vessel motions in the intact human subject. Various points on the borders of the cardiovascular silhouette have their own characteristic motions, atrial, ventricular, venous, arterial, or combinations of two or more such motions. These motions may be characteristically altered in the presence of cardiovascular disease.

Roentgen kymography has been used for the study of heart border motion but has failed to satisfy all requirements. The curves of motion on the roentgen kymograms are of small size and lack detail. (Their lack of definition precludes the effective use of optical magnification.) Roentgen kymograms are necessarily brief. Electro-kymograms, in contrast, are tracings with all the amplitude and detail of the familiar electrocardiograph and may be run continuously for as long as is feasible for an ordinary fluoroscopic study of the patient's heart. In fact, electrokymography of heart border motion is accomplished with a fluoroscopic X-ray beam of ordinary routine intensity.

The interpretation of electrokymograms of the various cardiovascular border motions is facilitated by simultaneous recording of the carotid pulse, on the same strip of bromide paper, through the same lens system as is used for the string galvanometer of the electrokymograph. By such means we have been able to identify five to six distinct phases in the motion curve of the left ventricle. Distinct phases are also demonstrable in the motion curve of other portions of the cardiovascular silhouette. Electro-kymograms of motion of the left ventricular border are surprisingly like typical ventricular

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volume curves. Likewise, electrokymograms from the borders of the pulmonary artery and aorta are surprising replicas of the typical pressure curves from these vessels.

Electrokymograms have been found to be quite characteristic in cases of premature ventricular systoles, bigeminal rhythm, auricular fibrillation, bundle branch block, mechanical alternans, and myocardial infarction.

BRULL, LUCIEN (Liège). *Surgical treatment of experimental uremia.*

Salts of heavy metals (mercury, gold, uranium) produce toxic nephrosis and uremia when given in sufficient amounts, conditions which are similar to those which eventually occur in man. For many years we have been considering the experimental relief of toxic uremia. By means of kidney implantation in the neck with Payr's canulae, according to a technique which we used since 1931 (*C. R. Soc. Biol.* **107**, 248, 1931) for many experimental purposes, we were able to show in acute experiments (*ibid.* **118**, 811, 1935) that such kidneys may excrete within a short time the urea retained in the intoxicated dog. It is well known that when the intoxicated animal survives the stage of acute uremia, the kidney may recover its functions. The problem is to help the animal through the stage during which its own kidneys are out of action in order to provide more time for anatomical recovery.

Series of aseptic kidney transplantations were performed in dogs by myself and Dr. L. Lefébvre, using brass and later on vitallium canulae. Dogs were nephrectomised and when in full uremia after 24 or 48 hours, a normal kidney was implanted in the neck. The ureter was catheterized with a glass or plastic canula. In some experiments the transplanted kidney survived for five days.

The end of the preparation was due to several mechanisms: thrombosis of the arteries or veins, infection, loosening of ligatures, eventually stopping of the secretion of the transplanted kidneys.

The kidneys start secreting as soon as connected; they respond normally to water diuresis. Urea figures in blood drop by about one or two grams within 24-36 hours. The dogs do not try to remove the implanted organ, although no special protection is provided.

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We have shown previously (*Arch. Intern. Physiol.* 2, 257, 1940—*Brull, L. and Dor, M.*) that kidneys from dogs killed up to one hour before and transplanted into living animals recover within a few minutes their functions. Such kidneys may be used for surgical treatment of toxic uremia.

CHAUCHARD, B., and CHAUCHARD, P. (Châtillon-sous-Bagneux). **L'Électrotonus somatogène, une propriété nouvelle des péricaryones neuroniques.**

Quand on exerce une action (pharmacologique, électrique) localisée sur une fibre nerveuse, on n'observe que des perturbations fonctionnelles localisées, par exemple une variation de chronaxie. Poursuivant nos recherches sur les mécanismes des processus de subordination de *L. et M. Lapicque*, variations de chronaxie des nerfs commandées à distance par les centres nerveux, nous avons étudié les effets d'une agression s'exerçant sur les péricaryones (sensitifs dans un ganglion spinal, sympathiques postganglionnaires dans un ganglion sympathique, moteurs volontaires et sympathiques préganglionnaires dans la moelle). Si on applique à ce niveau soit une solution diluée d'une substance active sur le neurone (nicotine, aneurine, etc. . .), soit une anode ou une cathode (l'autre électrode étant dans les tissus voisins), on constate une variation de chronaxie généralisée à l'ensemble du neurone jusqu'en ses plus lointaines fibres, et à lui seulement (possibilité de distinguer les fibres diverses d'un même nerf). C'est suivant l'expression de *L. Lapicque*, un *électrotonus somatogène*, soit un pouvoir spécial que possède le péricaryone de régler la chronaxie de tout le neurone en modulant la valeur de sa polarisation. Il existe une action anélectrotonique avec diminution de chronaxie et une action catélectrotonique avec augmentation; l'amplitude multipliant ou divisant de 5 à 10 fois les chiffres normaux. La propagation s'effectue suivant un mode électrotonique indépendant de l'influx: une ligature qui arrête celui-ci n'empêche pas la métachronose somatogène, que seule interrompt la section du nerf.

Cette fonction du péricaryone, en rapport avec son pouvoir trophique, qui apporte un nouvel appui à la notion de neurone, seule différence importante entre fibre et corps neuronique, est normalement mise en jeu par les neurones centraux spéciaux de la

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subordination, ce que montre en particulier l'étude d'une galvanisation médullaire longitudinale (effets inverses des courants ascendants et descendants).

Indiquons que le phénomène ne se produit que si le péricaryone est intact; il disparaît par lésion, hémorragie ou action toxique ou électrique trop intense.

Comme dans l'électrotonus, la métachronose s'accompagne de modifications de toutes les propriétés de la fibre: le temps utile varie comme la chronaxie; la sensibilité pharmacologique locale des fibres est modifiée et on peut à volonté par cette action centrale à distance faire apparaître ou disparaître l'effet d'une intoxication locale de la fibre (par exemple nicotine pour les fibres sympathiques ou effet lésant d'une ligature).

Ajoutons que cette modification somatogène de la polarisation neuronique entraîne des changements dans le taux de médiateur chimique libéré à la périphérie pour les neurones ganglionnaires sympathiques, curieux exemple d'une variation de médiateur non liée à l'influx.

¹ Pour plus de détails, voir P. Chauchard, *Revue Scientifique*, 83, 89-98 (1945), et B. et P. Chauchard, *C. R. Soc. Biol.*, 22 février 1947.

BURRIDGE, W. (Rangoon). *The physiological atom.*

Inanimate objects set in terrestrial motion obey the law of natural stimulation discovered by stimulating beating hearts with adrenaline, viz. in living structures their natural stimulation according to its strength causes a corresponding development of energy which first remains in being and then dissipates after the stimulant has ceased to act. The natural stimulation of beating hearts, it should be observed, has its analogies in the effects which follow on pressing down a motor-car's accelerator pedal and not in those of sparking the gases.

The similarities show that the augmented functional capacity exhibited by naturally stimulated tissues depends on an increased velocity of surfaced particles moving in a frictional medium. Colloids were first examined as the moving particles, because of Brownian movement, and deemed to move in the ordered fashion

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of a regiment at drill whereas Brownian movement corresponded with that of a crowd on the same parade ground.

The combustion of stimulants, however, could not supply the increased energy manifested by stimulated tissues. Hence the particles are self-propelled. Since also increased functional capacity does not travel, while an excitation does, the range of movement of the particles must be limited. But restriction by boundaries was found to confer on living matter the properties of a gas while orderly movements of the parade-ground type required additional forces to give an about-turn. Also there could be no halting or marking time because the law indicates that the particles are always in movement.

An orbital system met requirements. Spherical or regularly shaped self-propelled satellites are not, however, compatible with orbital stability in a frictional medium, and any other shape would provide ruddered satellites capable of moving in their own circles.

Colloids were thus ruled out as moving satellites but a salt-colloid complex of the type investigated by Macdonald meets nuclear requirements. Its coagulative neutralization would set in action forces leading to its own reconstitution, and set satellites free to wander in their own circles, which would be greater than their orbits. They would therefore wander into neighbouring systems and disrupt them. The satellites develop a frictional electric charge varying with their speed and opposite to that of the nucleus.

With excitation as disruption of the orbital system, provision is made for (a) spread of excitation in all directions; (b) excitable tissues to behave as wound-up springs which automatically re-wind; (c) metabolic provision of energy; (d) a 10° C. rise to double the rate of metabolism, but with friction preventing a doubling of functional capacity or speed.

CHEN, K. K. (Indianapolis). **Digitalis-like substances.**

Twenty-one compounds which have a digitalis-like action were each assayed in groups of cats for comparison of their potency, as shown in the following table:

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Compound	Mean (Geometric) Lethal Dose \pm Standard Error:	
	$\mu\text{g. per kg.}$	
Adonitoxin	191.3 \pm	17.5
Cymarol	99.4 \pm	6.51
Glycoside A of <i>Strophanthus sarmentosus</i>	112.3 \pm	5.38
Glycoside B of <i>Strophanthus sarmentosus</i>	16572 failed to kill	
Cheirotoxin	118.5 \pm	3.60
Convalloside	215.0 \pm	13.2
Desgluco-hellebrin	86.1 \pm	3.70
Evonoside	838.7 \pm	119.5
3-Methoxyacetyl strophanthidin	334.5 \pm	29.5
3-Diethylacetyl strophanthidin	1047 \pm	125.3
3-Trimethylacetyl strophanthidin	1799 \pm	188
3-Bromoacetyl strophanthidin	7803	
3-Iodoacetyl strophanthidin	677.8 \pm	19.5
3-Trichloroacetyl strophanthidin	453.9 \pm	27.9
3-Phenylacetyl strophanthidin	1061 \pm	89.1
3-Phenoxyacetyl strophanthidin	334.8 \pm	48.7
3-Dimethylaminoacetyl strophanthidin	266.3 \pm	22.7
3-Diethylaminoacetyl strophanthidin	262.9 \pm	40.5
3-Di-n-propylaminoacetyl strophanthidin	355.4 \pm	47.9
3-Di-n-butylaminoacetyl strophanthidin	704.5 \pm	78.9
3-Chloroacetyl anhydrostrophanthidin	17120 failed to kill	

The first eight glycosides were supplied by Professor T. Reichstein, Basel, and the last six by Professor Robert C. Elderfield, New York City. The remaining seven derivatives of strophanthidin were prepared in our own laboratory. The results as shown in the table afford a good opportunity to correlate, as far as possible, chemical structure and cardiac activity.

Studies were also made in frogs with adonitoxin, cymarol, glycoside A of *Strophanthus sarmentosus*, cheirotoxin, convalloside, and desgluco-hellebrin. Experiments were carried out to test the absorbability of these substances and their duration of action, but the results were as yet inconclusive.

DALY, I. DE BURGH, DUKE, H., and WEATHERALL, J. (Edinburgh). **Pulmonary vasomotor nerves.**

The functional activity of pulmonary vasomotor nerve fibres issuing from the upper thoracic sympathetic chain has been tested in the perfused living animal (dog) preparation. In this preparation the heart ventricles are replaced by two blood pumps and conditions are established for the separate study of the systemic and pulmonary circulations. Mechanical, nervous, and humoral processes regulating the state of the two circulations can be investigated independently without the complication of changes in heart output. The replacement of the two heart ventricles by the two separate pumps is effected whilst the systemic arterial pressure remains within normal physiological limits. The respiratory centre and pulmonary vasomotor responses may remain active up to 8 hours of perfusion.

Stimulation of the upper sympathetic chain, the stellate ganglion, or the middle cervical ganglion may cause pulmonary vasoconstriction or vasodilatation. The cell stations for both types of fibre reside in the stellate and in the middle cervical ganglia. Under the conditions of our experiments a pulmonary vasoconstrictor response to sympathetic stimulation is more common than a dilator response. The pressure changes following unilateral stimulation amount to 10-25% of the initial pulmonary arterial pressure.

The constrictor response has been obtained under the following conditions in fully atropinised animals: (1) during the absence of artificial ventilation; (2) with positive or negative pressure ventilation; (3) in the absence of bronchomotor effects; and (4) at zero systemic arterial pressure. The last-named condition eliminates the possibility that the pulmonary vasoconstriction is due to an increase in the amount of blood transferred from the bronchial vascular system to the pulmonary vascular system.

The activity of the pulmonary vasoconstrictor or of the vasodilator fibres is not significantly influenced by eserine or by atropine. The constrictor response is suppressed or reversed by ergotoxine ethanesulphonate. The evidence obtained is not incompatible with the view that the lungs are supplied with adrenergic vasoconstrictor and adrenergic vasodilator fibres.

The pulmonary arterial pressure rise following unilateral sympa-

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thetic stimulation is equivalent to approximately half that produced by occlusion of the pulmonary arterial branch to one lung.

The cervical vagosympathetic nerves also contain both pulmonary vasoconstrictor and vasodilator fibres. The origin and nature of these fibres have not been determined.

HARDY, J. D., SHORR, E., and DU BOIS, E. F. (New York). The influence of environmental temperature and estrogens on the basal metabolism of women.

Calorimeter observations on seven normal young women with regular menstrual cycles published in 1941¹ indicated that the basal metabolism, nude at an environmental temperature of 22° C., was about 13% higher than at a temperature of 30–32° C. One young woman with amenorrhea showed in this temperature range the level basal metabolism characteristic of men.

Since this publication 47 additional calorimeter observations have been made on 3 women. One young woman greatly undernourished with secondary amenorrhea demonstrated the same absence of rise in metabolism in the cold.

Two women about 50 years old with complete removal of ovaries and uterus were studied. One gave an average in the cold zone about 8% higher than in the warm zone and the same result was obtained when she was given estrogens. The other castrate showed the level basal metabolism characteristic of men but when given estrogens during her menopausal symptoms responded with the rise in cold environment characteristic of young women. Five years later the administration of estrogens was not accompanied by this response to cold.

Further studies are being made with and without estrogens and up to the present time no consistent estrogenic effect has been established. In an effort to find the details of temperature adjustment determinations are made of the total heat production, heat loss, skin temperature, peripheral blood flow, radiation, convection, and vaporization.

¹ Hardy, J. D., Milhorat, A. T., and Du Bois, E. F., *J. Nutrition*, 21, 383 (1941).

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FERGUSON, JOHN H. (Chapel Hill, N.C. (U.S.A.)). **Enzymes and enzyme-inhibitors in relation to blood coagulation.**

Making use of bacterial *kinase*-type activators, proteolytic enzymes of blood plasma (and products thereof) are obtained in the active state and tested both for their protein-lysing effects and their actions in relation to the blood-clotting system. A fibrinogen-lysis method is the basis for a sensitive enzyme-assay technic, by which can be followed both the activation of the protease and its inhibition by various agents, including crystalline trypsin-inhibitors from pancreas and soybean. In vitro clotting systems are constituted of purified reagents and it has been found that the active protease (*not* its kinase) has an important clot-aiding action of the 'thromboplastic' type. Proteolytic actions which modify the clotting mechanism apparently do not include thrombinolysis (with amounts of enzyme thus far tested).

A more potent tryptase, however, is thrombinolytic and this action is inhibited by trypsin inhibitor.

FISCHER, ERNST (Richmond, Va.). **Changes in protein during denervation atrophy and their retardation by appropriate electrical treatment.**

Total protein concentration diminishes by about 14% during denervation atrophy of 25 days' duration (rabbit). Collagen concentration increases about reciprocal with the weight loss, but the increase in collagen content is somewhat less than expected under the assumption that the amount of collagen present in the whole muscle remains constant. The amount of extractable actomyosin is diminished about 75% although non-collagenous protein is only decreased about 30%. The ratio of actin to myosin in actomyosin from denervated muscle is much higher than the ratio for normal actomyosin. In consequence, there exist distinct differences in the physicochemical properties of the two actomyosins.

Pure actin isolated according to Straub from normal and denervated muscles show no qualitative and only little quantitative differences. Myosin extracted according to Szent-Györgyi and purified by repeated precipitations decreases about 85%, while the crude

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myosin extract shows only a decrease of about 60% in protein content.

Crude myosin extracts from denervated muscle have much lower adenosinetriphosphatase activity than those from normal muscle. This decrease is not due to an increase in inhibitory substances. With purification, the ATPase activity of the myosin increases more distinctly for denervated than for normal muscle, but the ratio of precipitated protein to non-precipitated is much smaller for myosin from denervated muscles. In contrast to myosin from normal muscle, the non-precipitated fraction of myosin from denervated muscle has retained some ATPase activity. The most purified myosin obtainable from denervated muscle (25 days, 40% weight loss) has an ATPase activity of about two-thirds of normal myosin. Calculations of the total ATPase activity per gm. muscle from the ratio and the activities of the various fractions reveal that after 25 days the ATPase activity is only about 15% of that of normal muscle.

All these protein changes were brought about by denervation progress rather slowly for the first week, during which, as reported previously, also birefringence of the muscle fibers and total strength of the muscle per gm. muscle weight does not diminish appreciably despite the fact that a considerable weight loss occurs during the first week.

Daily treatment of denervated muscles with appropriate currents is effective in retarding not only the weight loss but also some of the protein changes. Treatment applied to a leg in a joint position, so that the muscle contracts against high resistance, is much more effective in retarding weight loss and protein changes than treatment in a position in which the muscle contracts freely against little or no resistance.

GANTT, W. H., HOFFMANN, W. C., and DWORKIN, S. (Baltimore). **The cardiac conditional reflex.**

That the heart beat is sensitive to strong emotional changes as well as to severe muscular exercise has long been known. What is its role in the conditional reflex independent of observable emotional states and of gross bodily movements? Cardiac rates were studied to

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auditory and visual stimuli before and after they were made signals (conditional stimuli) for an unconditional reflex (food or pain). Auditory or visual stimuli *per se* initially produced changes in heart rate (orienting reflex) which usually disappeared on repetition (Robinson). As these signals become transformed into conditional stimuli they evoke definite heart rate (HR) changes parallel to the salivary conditional reflex with food or the motor conditional reflex with pain. The modification of HR is specific for excitation and inhibition and for several other factors, e.g. amount of food (unconditional stimulus), on which the conditional reflex is based—thus the increased HR is greater to signal for large (10 gm.) than for small (1 gm.) amount of food. Dependent on the state of the animal, the cardiac conditional reflex disappears with satiation, parallel to the salivary conditional reflex. The cardiac conditional reflex to the signal for food was often as great as to the eating of food. It varied from individual to individual, ranging from an increase of 10 to 40 beats with 4 gm. food. (In some dogs the heart decelerated.) The respiratory rate generally paralleled the cardiac, but was not nearly as specific. The pattern of the changes are constant for a given individual. The cardiac conditional reflex apparently is the result of a central excitatory state; it occurs to an almost equal extent whether the dog is making any gross bodily movement. It is more sensitive than either the salivary or the motor reactions, with a shorter latent period and has the advantage of measuring the *degree* of inhibition, although it lacks the ease of quantitation of the salivary conditional reflex. It is more quickly formed but more difficult to extinguish (inhibit). Thus in an animal who apparently shows complete inhibition of a conditional reflex measured by both salivation and movements, there may be persistent cardiac changes to a former signal lasting for two years after apparent inhibition. The persistence of the internal visceral change with absence of the superficial motor reaction, as well as of salivation, provides the basis for dichotomy of function and mal-adaptation.

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GEMMILL, CHALMERS L. (Charlottesville, Va.). **Effect of alloxan and theobromine derivatives on glycolysis.**

The effect of alloxan and theobromine derivatives was studied on the anerobic glycolytic activity of extracts of muscles of the frog. The anerobic glycolysis of glycogen to lactic acid was measured by the production of carbon dioxide from bicarbonate using Warburg vessels and manometers. Alloxan inhibited the production of carbon dioxide under the conditions of these experiments. The degree of inhibition was proportional to the concentration of alloxan. The inhibitory activity of alloxan was reversed by the addition of cysteine to the reaction mixtures. The results of the theobromine derivatives on glycogen glycolysis could be divided into three groups: (1) giving a primary stimulation followed by a secondary inhibition, (2) giving inhibition, and (3) giving neither stimulation nor inhibition. In the first group are methyl (caffeine), ethyl, isoamyl, propyl, crotyl, methoxyethyl, and allyl; in the second group is butyl and in the third group methallyl theobromine. Theophylline, urethane, and 2-amino pyrimidine have no effect on the rate of glycolysis.

KUFFLER, S. W., and GERARD, R. W. (Chicago). **The small-nerve motor innervation to frog's skeletal muscle.**

Small diameter motor nerve fibers which emerge in the spinal ventral roots differ from the well-known large motor fibers in many properties and in function. In the frog, the small fibers, as compared with the large, range around 5μ diameter rather than 15μ , conduct at 22°C . at 4 to 8 m/sec. rather than 10 to 40, have a threshold 3- to 6-fold the most excitable large fibers, and are more easily blocked by novocaine and their neuromuscular junctions by curarine. The small fibers are not of sympathetic origin. A single small-nerve fiber normally innervates many muscle fibers, of which at least some also receive large-nerve motor innervation. Small-nerve motor activity is easily detected if large-nerve stimulation is avoided by (1) complete dissection isolation of small-nerve fibers, (2) pressure or polarization block of a trunk, or (3) appropriate reflex stimulation.

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A single stimulus to a small-nerve fiber evokes practically no mechanical muscle response. At frequencies above 3/sec., local contractions are observed in small transparent muscles, and at frequencies over 10/sec. distinct shortening and tension is set up in innervated muscles. Contractions are finely graded with stimulation frequency, are not propagated but local, confined to junctional regions, and are accompanied by potential changes (called small-nerve junctional potential, s.j.p.) which resemble the endplate potentials (e.p.p.'s) of curarized skeletal or normal crustacean muscles. The tension produced by the small-nerve system, evoked reflexly or by direct small-nerve stimulation, can reach at least 10 to 20% of the maximal single twitch tension. The small-fiber tension is optimal at lower resting tensions than is optimal for a maximal twitch. When the nerve to, say, the semitendinosus is briefly tetanized with stimuli which excite the small nerve fibers as well as the large, and not when the large only are stimulated, a prolonged feeble tension outlasts the tetanic shortening.

Small nerve discharges are frequently present during apparent rest in spinal or lightly anaesthetized frogs and s.j.p.'s can be recorded from the surfaces of many muscles. When all disturbance is carefully avoided these fade out. Appropriate reflex stimulation can augment or inhibit these discharges. Reflex activation is obtained from touch to the skin rather than stretch of muscles, and results from electrical excitation of cut ipsilateral or contralateral nerves. In the case of nerve stimulation, small-fiber reflexes appear without the usual motor twitch responses, when stimuli are of low intensity and frequency.

GLEES, F. P., LIDDELL, E. G. T., and PHILLIPS, C. G. (Oxford).

Postural and motor functions of supraspinal nerve levels.

The effects have been studied, on the posture and locomotion of cats, of pyramidal section, decortication, excision of the sigmoid gyri, electrolysis stereotactically of the caudate and the lenticular nuclei, severally or combined. Observation ranged from periods of three weeks to seven years, with terminal histological definition of the lesions. Simple locomotion such as walking on the floor was

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compared with ability for more skilled motor performances such as jumping, climbing, chasing a ball of paper, and walking along the rungs of a horizontal ladder. Cinematographic records have been made.

None of these functions is seriously disturbed by any single lesion, although the most vulnerable locus is the cortex cerebri. Even combination of striatal with pyramidal or pyramidal with cortical lesion did not often cause much disability of simple locomotion, across a level floor, but did produce serious derangement of more skilled performances such as walking on a ladder or up a wire net. A constant feature is crossed extensor hypertonia, which becomes apparent when the animal is suspended above the ground, but this hypertonia is largely or completely suppressed in simple locomotion and interferes hardly at all with it.

Our conclusion is that in the cat simple locomotion is performed without any constant over-riding control coming from the cortex cerebri or basal ganglia, or via the pyramidal tract. Moreover, disabilities, which might be expected as a result of their absence or dysfunction to interfere with locomotion, tend to be overcome so that spino-medullary levels perform simple locomotion correctly. On the other hand, movements more complex than simple locomotion need these higher loci for their accurate performance.

HALDANE, J. B. S. (London). **The action of high-pressure oxygen on man.**

When a human being breathes oxygen under pressure, the first symptoms observed may be pulmonary or nervous. Thus *Case* and *Haldane*, both unusually resistant to the nervous effects, noticed bronchial irritation after 370 minutes at $2\frac{1}{2}$ atmospheres, and had definite though slight bronchitis after 520 minutes. In many people at this pressure, and in all at higher pressures, nervous symptoms occurred before pulmonary. These symptoms included epileptiform convulsions with loss of consciousness, jactitation or diaphragmatic clonus without loss of consciousness, tonus followed by fibrillation of facial muscles, and a variety of subjective symptoms, including visual hallucinations, but not mental confusion. Though

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there were usually warning symptoms before a convulsion, this was not always so.

The time of onset was extremely variable. Thus in 17 experiments at 3.7 atmospheres, *Spurway* lasted an average of 45 minutes, but the times varied from 13 minutes with a convulsion to 88 minutes with only facial twitching. The differences between individuals were very great, and *Haldane* was so far sensitized after a year's experiments that he developed jactitation within 6 minutes at atmospheric pressure.

The sensitivity to high-pressure oxygen was markedly increased by exercise, by carbon dioxide at partial pressures above 3% of an atmosphere, and by other influences. The pulse rate was not always affected, but sometimes fell below 40 per minute.

HARVEY, A. M., GROB, D., LILIENTHAL, J. L., Jr., and JONES, B. F. (Baltimore, Md.). Observations on the effects of di-isopropylfluorophosphate on human subjects.

Di-isopropylfluorophosphate (DFP) inhibits cholinesterase (ChE) activity irreversibly. The effects of DFP have been studied in over 100 human subjects.

The ChE activity of plasma, which is exquisitely sensitive to DFP, falls precipitately to 10% of control level after the injection of 0.5 to 3 mg. of DFP. The regeneration of plasma ChE after DFP was depressed in subjects with hepatic disease indicating that this protein enzyme is elaborated at least in part in the liver. The ChE activity of the erythrocyte was less sensitive to DFP but continued administration produced profound depression. The regeneration of erythrocytic ChE proceeded in linear fashion with reappearance of 1% of control activity each day, a value equivalent to the daily production of new erythrocytes.

The administration of single large doses of DFP (2-3 mg.) or repeated smaller daily doses (1-2 mg.) produced a train of symptoms which mimicked the effects of cholinergic substances except that peripheral vasodilatation and hypotension were not noted. There was heightened activity of the gut, weakness and fasciculation in

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skeletal muscle, and many signs of increased excitability of the central nervous system.

The action of DFP on the gut was measured by intubation of both small and large intestine which revealed that the bowel developed great spontaneous overactivity which persisted for 4-6 hours after a single dose. Although spontaneous overactivity subsided then, the gut retained for days an exquisite sensitivity to minute doses of DFP and other stimulating substances (neostigmine, pitressin). The spontaneous activity due to DFP was suppressed temporarily by various depressing substances (atropine, morphine, demerol).

The action of DFP on neuromuscular function was studied by intra-arterial (brachial) injection and recording of the electromyogram in response to maximal stimuli of the motor nerve. DFP produced fasciculations, sweating, and profound motor weakness restricted to the injected area and these phenomena persisted for days. The accompanying electromyographic phenomena were repetitive responses to single stimuli, depression of the second response to paired stimuli and fluctuating responses to a train of stimuli. Pre-treatment with neostigmine blocked the action of DFP, but when administered after DFP intensified the latter's effects.

The daily administration of DFP produced the following changes in the electroencephalogram: increased frequency and potential, increased beta rhythm and large slow waves compatible with epilepsy. These abnormalities were suppressed immediately by the intravenous injection of atropine. The administration of DFP to two subjects with spastic paraplegia of the legs produced greatly increased spasticity in the legs without changes elsewhere. These effects of DFP, a lipoid soluble anticholinesterase which penetrates the central nervous system, are compatible with the hypothesis that the acetylcholine cycle plays an important role in central neural function.

HAWKINS, R., and MENDEL, B. (Toronto). The selective inhibition of pseudo-cholinesterase by diisopropyl fluorophosphonate.

Diisopropyl fluorophosphonate can inhibit both true cholinesterase and pseudo-cholinesterase but lower concentrations of this com-

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pound are required for the inhibition of pseudo-cholinesterase than of true cholinesterase. With appropriate concentrations of diisopropyl fluorophosphonate it is therefore possible to inhibit selectively, in a mixture of pseudo-cholinesterase and true cholinesterase, the activity of pseudo-cholinesterase without affecting the activity of true cholinesterase.

Since acetylcholine is hydrolysed *in vitro* not only by true cholinesterase but also by pseudo-cholinesterase, measurements of cholinesterase activity in which acetylcholine is used as substrate can yield no information regarding a correlation between the degree of inhibition of true cholinesterase by diisopropyl fluorophosphonate and the effects resulting from this inhibition *in vivo*. True cholinesterase is the enzyme responsible for the hydrolysis of the acetylcholine released at nerve endings and it is the degree of inhibition of this enzyme which must be determined when a correlation between anticholinesterase action and pharmacological effects is sought.

HIGGINS, GEORGE M. (Rochester, Minn.). Effect of synthetic lactobacillus casei factor on the blood changes induced by gastrectomy in the rat.

Synthetic *L. casei* factor (folic acid) has proved effective in controlling certain clinical as well as experimental anemias. Granulocytopenia, induced in animals by giving sulfonamides or sulfones, was corrected by *L. casei* factor. Granulocytopenia, often occurring spontaneously in animals, was corrected by the factor. Neutropenias induced by bone marrow depressants, however, did not respond. Those blood dyscrasias, induced by drugs which alter the bacterial flora, appear to improve by the administration of *L. casei* factor.

The total removal of the stomach from rats incites a severe blood dyscrasia. This includes microcytosis, lowered hemoglobin level and reduced granulocyte count. Ferric ammonium citrate improves the blood picture. When given with liver protein the dyscrasia may be entirely corrected. This report covers the results of giving *L. casei* factor to gastrectomized rats in which a microcytic hypochromic anemia had persisted for five months.

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Twenty-four healthy adult male rats, weighing from 310 to 320 gm., were selected. Sixteen were gastrectomized; eight were not gastrectomized, serving as controls. All were fed a purified diet, of sucrose, vitamin-free casein, corn oil, and a salt mix. All vitamins were adequately provided. Food intake was recorded. Animals were weighed at frequent intervals. Blood, obtained from the heart, was sampled at three, six, twelve, and twenty weeks after operation. After the last sampling L. casei factor (kindly furnished by Lederle Laboratories, Inc.) was provided in the diet, at a level of 100 micrograms per gm. for fourteen days; the blood was again sampled. L. casei factor was then given intraperitoneally (400 micrograms per day) for fourteen days. The blood data were given assembled.

Results: (1) Gastrectomized rats consumed on the average 15% less calories than their non-gastrectomized controls. (2) Gastrectomized rats gained weight for several weeks after operation but then rapidly lost weight, although taking adequate amounts of food. (3) The administration of L. casei factor, either in the diet or parenterally, did not change the erythrocyte count, the erythrocyte size, or the hemoglobin level of gastrectomized rats. The total number of granulocytes increased from 1,900 per cubic millimeter to 7,200 when the vitamin was given in the diet and to 11,100 when given parenterally. L. casei factor was without effect on the number or size of erythrocytes but induced marked stimulation of all myeloid elements.

HIMWICH, H. E., HIMWICH, W. A. (Edgewood), and ETSTEN, B. (Albany, N.Y.). **The functional organization of the central nervous system as observed in pentothal anesthesia.**

In previous work on patients receiving the insulin treatment for schizophrenia we found that the symptoms of hypoglycemia appeared in groups which as a working hypothesis may be linked with the functional pattern of different levels in the neuraxis. In the present investigation of pentothal anesthesia a similar symptomatic analysis was made and in addition, the physiologic basis for the clinical changes was studied. Blood was drawn simultaneously from both internal jugular veins and the femoral artery to determine:

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(1) the right and left cerebral AVO₂ differences and (2) the right and left cerebral blood flows according to the method of Kety and Schmidt, both (1) and (2) being necessary to calculate cerebral metabolic rate. The cerebral oxygen utilized was greater on one side than on the other with average values of 3.9 cc. oxygen/100 gm. tissue/minute and 2.7 cc. oxygen/100 gm. tissue/minute. Because of the asymmetric distribution of the cerebral venous return it was concluded that the higher value includes the metabolic component of the cerebral hemispheres.

The subjects were anesthetized with a 1% solution of pentothal administered intravenously. The induction of the anesthesia was intentionally slow in order to avoid the telescoping of the stages which usually occurs during a fast induction. The average rate during anesthesia is 2.1 cc. oxygen/100 gm. tissue/minute, a reduction of 36% from the control value. The reduction in metabolism was not equal throughout the brain. The pattern of pentothal anesthesia shows that cortical oxidations are depressed earlier and more profoundly than those of the rest of the brain. The clinical signs exhibited a similar progression down the neuraxis starting with the cerebral hemispheres, Stage I, Clouding, and then through a series of steps gradually extending to the medulla oblongata: Stage II, Hypersensitivity; Stage III, Surgical Anesthesia; Stage IV, Impending Failure. The clinical changes may be explained in part by a descending inhibition of cerebral oxidations but because some of the signs appear to be out of proportion to the metabolic depression it is concluded that a second factor, specific effect on nerve function, is also operative.

JACOBSON, EDMUND (Chicago). **The measurement and treatment of nervous states by physiological methods.**

This international meeting comes at a time when in every country many people have been left in a state of nervousness and emotion following the trials and tragedies of World War II and when many are still striving to adjust themselves to the changes which have been suffered and to the uncertain future. Therefore it seems altogether fitting and proper to submit here a cumulative summary of what progress has been made in this laboratory and in this clinic and

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previously in the Physiological Laboratory of the University of Chicago toward the development of a sounder understanding of nervous and emotional states in man, their measurement and their treatment, by methods which derive from physiology.

Like any other science, an applied physiology must depend upon measurement. Otherwise, divergent views, 'schools of thought', and unrecognized speculation will continue.

We have employed three successful systems: (1) amplifier-galvanometer assemblies (1928-32); (2) the neurovoltmeter, in which action-potentials are rectified; (3) the integrating neurovoltmeter, by which potentials can be plotted against time, eliminating photography.

Measurement furnishes objective criteria for diagnosis and for testing the value of any therapy.

In the intact organism, using platinum wire or surface electrodes, controlled measurements of nervous and mental phenomena require accuracy to a fraction of a microvolt. Limiting the frequency ranges, I have thus measured; (1) tonus and muscular contraction; (2) discharges in peripheral nerve in man without anesthetic; (3) the influence on normal individuals of certain stimulants and sedatives, and (4) uterine tonus and responses.

The electrophysiology of mental activities deserves special mention. Our evidence indicated that imagination, reflection, and other moments of mental activity are not confined to closed circuits within the brain, but are specific physiological, muscular acts.

The controls of the efforts of man, both 'mental' and physical, are his striated muscles. As these relax, especially when residual tension diminishes or disappears, reflexes decrease, the blood pressure falls, respiration becomes slow and shallow, spastic viscera relax and every system shows lowered activity, including 'the mind'.

Accordingly, we find that it is physiologically impossible to be nervous or emotional and relaxed at the same time. Since 1918, progressive relaxation has been applied to common nervous and psychiatric disorders, to fatigue states, to alimentary spasticity including colitis, to arterial hypertension, and other conditions. Cultivation of relaxed habits requires faithful practise. During the war, 15,000 Naval Air Cadets received this training. Doubtless relaxation technique belongs not only in the clinic; it should reach the masses through instruction in elementary and higher schools.

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JAQUES, L. B. (Saskatoon, Sask.). The use of silicones in controlling the coagulation of the blood.

The silicones are a group of complex polymers containing silicon, which possess marked water-repellant properties. Several of these have been tested for their effect on blood coagulation. It has been found that one of these (Dri-Film # 9987) when applied to glassware, &c., markedly delays the clotting of blood. This effect appears to be due to protecting the blood from the coagulant influence of foreign surface, since the blood clots normally when transferred to glass. The material can be applied to syringes, needles, cannulae, &c. The silicone surface does not prevent clotting due to thromboplastin released from damaged tissue. Hence it is necessary to prevent contamination of the blood with thromboplastin. Using this material with a suitable technique, it has been possible to obtain blood which remains unclotted for several hours, thus providing blood free of anticoagulants for physiological experiments. Blood thus prepared has been used as the perfusion medium for the isolated dog liver. This has permitted the demonstration of the significance of the blood in the liberation of histamine and heparin from the liver by peptone and also the study of factors affecting the blood platelets. Finally the material has been found of value in routine laboratory use in cannulae, &c.

DOBSON, E., KELLY, L., JONES, H., and GOFMAN, J. (Berkeley, Calif.). Radioactive substances specifically localized in liver, spleen, or bone marrow.

A colloidal form of chromic phosphate which is inert and nontoxic has been used by the authors for several years. Given intravenously it localizes specifically in the liver and spleen but where particle sizes are encountered that are large enough to occlude capillaries these particles are found in the lungs. Chromic phosphate has been used to give specific irradiation to the spleen and liver when injected intravenously. The efficiency of phagocytosis of this compound is great, so that practically all of it is removed in a single passage through the liver. It can be used experimentally for the indirect

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measurement of liver circulation. Other compounds of radioactive isotopes have been studied which have similar properties. Radioactive gold sol, suspensions of calcium phosphate, strontium phosphate, and ferric phosphate have a similar rapid uptake by the liver and spleen. These less inert substances dissolve and are translocated in the body whereas the chromic phosphate remains in the tissue indefinitely.

Colloids of yttrium and zirconium which are also inert have been prepared. Some of these go rapidly to the liver and spleen as do the above-mentioned colloids; some have a tendency to stay in the circulating blood for long periods of time; some seem to have high specificity to phagocytosis in the bone marrow. The distribution of colloids to liver, spleen, or bone marrow seems to depend upon some combination of physical properties which is as yet not understood.

Irradiation of the liver specifically by these colloids is usually tolerated in ranges of 500 to 100,000 r. in rats and mice when the radiation is from a single administration of radioactive chromic phosphate. Much destruction of liver tissue takes place with the upper dosages and the animal seems to recover only when sufficient time has elapsed to allow for elimination of radioactivity by decay and a subsequent regeneration of the lesser-irradiated peripheral edge of the liver. The bone marrow can be deleted by this form of radiation.

JONES, H., KELLY, L., and LAWRENCE, J. (Berkeley, Calif.). **The depression of desoxyribose nucleic acid metabolism by liver irradiation.**

Hevesy has reported an indirect effect of irradiation on the desoxyribose nucleic acid metabolism of neoplastic tissues. His work used bilateral tumors, one of which was irradiated, and he measured desoxyribose nucleic acid metabolism by the rate of radioactive phosphorus incorporation into desoxyribose nucleic acid.

Using radioactive colloids which localize in the liver, the liver was specifically irradiated in tumor-bearing animals. A great depression of desoxyribose nucleic acid metabolism was obtained in the neoplastic tissues when the dose of liver irradiation reached approxi-

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mately 2,000 to 3,000 r. and this effect appears to be the same whether the irradiation was expended in four hours or in two days. Animals injected with methylcholanthrene in colloidal form (0.5 of a milligram intravenously) showed an increase in desoxyribose nucleic acid metabolism.

JONES, H., DOBSON, E., and LAWRENCE, J. (Berkeley, Calif.).
Tracer studies of blood-tissue perfusion rates at rest and a new criterion of blood mixing times.

Inert gas exchange of the body and parts of the body is measured by exchange of body nitrogen and the use of radioactive inert gases, argon, krypton, and xenon. The resting circulation to muscle and connective tissue lies between 5 and 25 cc. of blood per liter tissue per minute. For fat it is less than 10 cc. of blood per liter tissue per minute. Radioactive colloids used in liver circulation studies place the blood tissue perfusion rate of the liver at approximately one volume of blood per liter per minute. Circulation of the thyroid as measured by the uptake of radioactive iodine is 10 volumes of blood per liter per minute. The circulation to the brain is measured by radioactive gas exchange as 0.7 volumes of blood per liter per minute.

The distribution of the cardiac output to the viscera in gas exchange experiments accounts for 70% of the cardiac output, and this is in accordance with the perfusion rates of the organs as reported here and obtained from the literature. The average perfusion rate of the carcass is less than 20 cc. per liter tissue per minute at rest. Gas exchange measurements during exercise show an increase in blood-muscle perfusion rate of 100 to 500 cc. per liter tissue per minute for heavy, steady-state exercise.

The rate of blood mixing at rest should theoretically be long considering the pool of blood that is contained in the carcass and the general level of the blood tissue perfusion rate of the carcass, compared to the rates of the body. The major circulatory pool, consisting of blood in the viscera, is being turned over quite rapidly since it constitutes approximately half of the blood volume and most of the cardiac output is distributed to these tissues. A radioactive

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colloid which stays in the blood temporarily has been used to show slow mixing streams in the carcass. Geiger counters placed over the legs as compared with the thorax and the splanchnic pool show that the apparent mixing rate in the rabbit is one to five minutes for arterial blood and heart blood. However, blood in the splanchnic pool remains somewhat richer than the general circulation in its content of radioactive colloid. Simultaneously with the equilibration of the richer splanchnic pool and the main circulatory stream, there seems to be a dilution by slowly mixing blood in the carcass. It is calculated that 75% of the blood perfusing the legs quickly moves through channels and freely equilibrates with the blood pool there. Another 5 or 10% mixes more slowly but still fast enough to be mixed in five minutes whereas there is a pool of blood amounting to 15% of the total blood contained in the carcass which is mixed at the rate of approximately 6% per minute or 60 cc. of new blood per liter of blood pool per minute. It is this fraction, which accounts for approximately 8% of the total blood volume, which would be extremely difficult to measure by the usual techniques of blood volume. Even in the normal resting state it may require 15 to 30 minutes of mixing to measure this fraction.

It is impossible to use the criterion of arterial-venous differences for determining blood mixing time in the carcass, as the blood in the carcass is not one uniform pool but rather is composed of three pools with different speeds of mixing, and the more rapidly mixed pools get the greater flow of blood so that the small differences that might be encountered, due to unmixed blood, are masked by the greater flow of blood through the rapidly mixed blood pools of the carcass.

JOSEPHSON, BERTIL (Stockholm). **A way to trace the paths of the blood from the small intestines in man.**

A substance, such as tetra-iodine-phenolphthalein or a bile acid, which is transferred from the intestines to its blood vessels and which is completely removed by the liver from the portal blood will normally never appear in the peripheral blood. If the intestinal blood is shunted over into collateral veins which do not carry it to the liver, it will appear in the circulating blood. Thus, if the sub-

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stance is able to be excreted by the kidneys, it will appear in the urine. In this way the existence of a collateral circulation of the intestinal blood can be traced, even if the proportion of shunted blood is small. This may be of interest also from a clinical point of view. In this way it has been possible to demonstrate collateral blood-circulation in the early stages of liver cirrhosis. The patients and the experimental animals were given a suitable amount of tetra-iodine-phenolphthalein and the iodine content of the urine was determined. After the administration no iodine could be found in the urine of normal men and animals. In cases with collateral circulation the amount of iodine appearing in the urine seemed to be roughly proportional to the amount of blood shunted over. Similar experiments with bile acids are in progress.

LECOQ, RAOUL (Saint-Germain-en-Laye). *Formes alcalosiques et acidosiques du rachitisme osseux.*

On admet, d'une manière générale que la production du rachitisme expérimental chez le rat blanc nécessite à la fois un déséquilibre phosphocalcique (par exagération du rapport Ca/P) et l'absence de vitamine D dans le régime, les sujets étant maintenus à l'obscurité pour prévenir toute synthèse de la vitamine D dans l'organisme.

Caractérisé par des lésions osseuses typiques, ce rachitisme comporte une alcalinisation du tractus digestif et des fèces, entraînant d'ailleurs rapidement une augmentation de la réserve alcaline sanguine et une augmentation du pH des os devenus inaptes à fixer le calcium. Par exemple: l'articulation fémoro-tibiale dont la réaction ionique est normalement de pH 7,5, monte à 7,7; 7,8; 8,0 et même 8,1. Une preuve supplémentaire de la nature *alcalosique* d'un tel rachitisme est fournie par la production de lésions osseuses rachitiques chez le rat recevant une alimentation privée de vitamine D, simplement additionnée de 3% de bicarbonate ou de citrate de sodium. Il paraît correspondre assez exactement au rachitisme des nourrissons prématurément sevrés.

A côté de ce rachitisme proprement alcalosique, nous avons montré qu'il est aisé de produire sur le rat diverses variétés de rachitismes, se développant à la lumière du jour (uviorésistants), et

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qui présentent tous une chute de la réaction ionique des os atteints, le pH 7,5 tombant alors à 7,3; 7,1; parfois même 7,0; la réserve alcaline pouvant parallèlement descendre, elle aussi, à des taux très bas.

Ces rachitismes *acidosiques* s'obtiennent par la simple suppression du sel calcique alcalogène des régimes rachitigènes classiques ou encore par la substitution à ce sel d'un sel calcique acidogène ou d'un sel acidogène non calcique. On peut arriver aux mêmes résultats avec un régime renfermant 2 % de carbonate de strontium, peu minéralisé par ailleurs, ou avec un régime présentant un rapport phosphocalcique normal mais retenant à la fois un sel acidogène (chlorure d'ammonium) et du lactose. C'est à ces formes acidosiques que doivent être rapportés les cas de rachitisme survenant chez les jeunes enfants (vivant parfois en milieux très isolés) sous l'action d'infections ou d'intoxications variées.

Qu'il soit acidosique ou alcalosique, le rachitisme cède aussi bien à l'action curative de la vitamine D. On note alors sur les articulations osseuses lésées une chute de l'activité phosphatasique alcaline, avec hypercorrection sous l'action du calciférol. Mais le taux de phosphatase alcaline diminue dans l'intestin et le rein des sujets atteints de rachitisme acidosique, tandis qu'il augmente avec le rachitisme alcalosique.

MCDOWALL, R. J. S. (London). A function of the venules.

In studies of vaso-constriction of the limbs of cats rested under chloralose, it has been found that changes in venous out-flow do not always correspond to changes in limb volume such as might be expected. In the intact limb, vaso-constriction shows itself by diminished volume accompanied by an increased venous out-flow, followed by a reduction. In the skinned limb, however, when vaso-constriction is brought about by a reduction of the depressor reflexes, e.g. by clipping off the carotid sinuses, a slight increase of limb volume or no change (*McDougall and McDowall, 1936*) is the usual result but a reduction of venous flow predominates, the preliminary increase being negligible or absent. The occurrence of such a reduction of venous flow in spite of a raised arterial pressure, together

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with an increase, or no change in skinned limb volume can only be accounted for by a constriction of venules and veins which has been shown by many workers to be under the control of depressor reflexes.

We may thus recognize three degrees of vaso-constriction in a limb, which depend on how the vaso-constrictor centre is stimulated: one, affecting primarily the skin vessels as a blood depot, which drives more blood into the circulation and raises the venous pressure partly in this way and partly by constricting veins (*Hooker*, 1918); two, best seen when the skin is removed, when the venules, and probably the arterioles, constrict and maintain the peripheral resistance without reducing the amount of blood in the muscles, and three, seen only as the result of very severe stimulation of the vaso-motor centre, e.g. by asphyxia, in which a reduction of the limb volume and venous out-flow occur together. Any severe but temporary vaso-constriction of the limb is commonly followed by a reactive hyperaemia.

It may well be that this function of the venules in retaining blood in the muscles is of considerable advantage as a preliminary to exercise before local dilating mechanisms become effective.

MACLEOD, JOHN (New York, N.Y.). **Certain aspects of the metabolism and motility of human spermatozoa.**

There are certain characteristics of the metabolism of human spermatozoa which make these cells unique among the mammalian cells of this type so far studied. Chief among these are a very low oxygen consumption which is in striking contrast to the high aerobic and anaerobic glycolysis. They also show a marked sensitivity towards high oxygen tensions inasmuch as motile activity may fail in oxygen whereas it is maintained for relatively long periods in nitrogen. The mechanism of the failure of motility in oxygen has been shown to be the production of small amounts of hydrogen peroxide, the latter being exceedingly toxic. Hemoglobin or catalase protects the spermatozoa against the failure of motility in oxygen.

New evidence will be presented to show that penicillin is a protective substance and the probable mechanism of its action in this regard will be discussed.

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The role of sulfhydryl groups in the energy systems which maintain motile activity has been investigated. In every case studied, substances which are known to inhibit the action of enzymes containing sulfhydryl groups also destroy the motility of human spermatozoa. A failure of glycolysis accompanies the loss of motility.

MASON, E. C., and RICHARDSON, D. L. (Oklahoma). **Traumatized muscle tissue as a factor in the production of shock.**

The blood pressure response to the administration of (1) *fresh tissue extract*, (2) *autolyzed tissue extract*, and (3) *tissue extracts containing bacterial metabolites* was recorded.

All the records were obtained from dogs varying in weight from ten to twenty kilograms. They were anesthetized with sodium pentobarbital (nembutal), approximately 0.03 grams per kilo body weight, injected intravenously, and additional injections were made as necessary to maintain the anesthetic level. Blood pressure records were obtained by cannulating the right carotid artery and connecting the cannula to a mercury manometer by means of rubber tubing, and the entire system was filled with sodium citrate solution. The respiratory movements were recorded by securing a stethograph drum to the chest.

In preparing the fresh muscle tissue extract, muscle tissue was obtained from dogs under nembutal anesthesia: the tissue was removed from the thigh and gluteal regions. Care was taken to remove only muscle tissue, in so far as it was possible, and ordinary precautions were taken to prevent the introduction of outside contaminating factors. The muscle tissue was immediately cut into smaller pieces and ground in a meat chopper. One volume of physiological saline solution was added to one volume of the ground muscle tissue; the mixture was put into an Erlenmeyer flask, stoppered and thoroughly mixed. The muscle-saline preparation then was kept at icebox temperature, approximately 5° C.; subsequently it was filtered through several thicknesses of gauze and the filtrate used for intravenous injections. Autolyzed tissue extract and tissue extract containing bacterial metabolites were obtained by incubating the fresh tissue extract, with and without the presence of antiseptics.

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Analysis of the experimental data led to the following conclusions:

(1) Extracts of fresh muscle tissue, administered intravenously, produced little change in blood pressure. (2) The administration of the filtrate obtained from the ground muscle incubated with penicillin also produced little if any change in blood pressure. (3) The filtrate of muscle tissue incubated with sulphadiazine produced a marked lowering of blood pressure, the drop being equal to approximately one-half of the original pressure. (4) Extracts of muscle tissue incubated without the presence of any antiseptic produced a fall in blood pressure followed by a secondary rise. The increased blood pressure was often double the original pressure. (5) The blood pressure response to incubated muscle tissue, without the presence of an antiseptic, is practically identical with that we have previously reported when using extracts of liver tissue which had been sectioned and left free within the abdomen. (6) Administration of the saline solution extract of burned fresh muscle tissue produced little if any change in blood pressure.

MAY, R. M. (Paris). Les combinaisons soufrées du nerf au cours de sa dégénérescence.

Nous avons provoqué la dégénérescence d'un nerf sciatique chez le chien et le lapin, et l'avons prélevé, ainsi que le nerf contralatéral, témoin, de 7 à 39 jours après l'opération. Nous avons dosé l'eau, le soufre total et les combinaisons soufrées lipidique, soluble dans l'alcool, protidique et hydro-soluble. Les segments et fractions de nerfs ont été minéralisés par la méthode de Wolf et Osterberg et les sulfates, précipités par du chlorure de baryum, ont été filtrés sur des tubes de Pregl en quartz, et pesés.

Il y a augmentation de l'eau au début de la dégénérescence, et augmentation progressive au cours du mois qui suit l'opération du soufre total (43.8 % — 0.433 % contre 0.301 % dans le nerf sain), lipidique (48.2 %), et hydro-soluble (70.3 %).

Il y a une augmentation réelle, et non pas relative à la baisse en poids sec du nerf dégénéré, du soufre total et hydro-soluble au cours de sa dégradation. Le soufre hydro-soluble existe également en plus grande quantité dans un cerveau de souris nouveau-né que dans celui d'une souris adulte.

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Il n'est pas exclu que des combinaisons soufrées hydro-solubles jouent un rôle comme substances neurotropes dans la régénération nerveuse.

MAZOUÉ, H., CHAUCHARD, P., et LECOQ, R. (Paris). Quelques propriétés vitaminiques et pharmacodynamiques de l'acide folique.

L'acide folique, vitamine indispensable au développement de divers microbes dont les effets antianémiques sont bien connus, s'est révélé jouer simultanément de l'activité vitaminique de la thiamine et de la riboflavine,¹ en raison de la nature ptéridinique de sa molécule.

Son étude au moyen de l'analyse chronaximétrique, qui permet la mise en évidence de très légers troubles neuromusculaires et peut servir de test précieux dans de nombreux domaines,² s'est montrée particulièrement intéressante. Comme les autres vitamines,³ il possède à doses faibles (quelques microgrammes) une activité pharmacodynamique intense sur le système nerveux normal en dehors de toute carence (action diphasique d'excitation, puis de dépression des centres supérieurs); par administration répétée, on arrive à un état dépressif permanent en rapport, comme dans le cas des vitamines B, avec de l'hyperglycémie.

L'acide folique peut remplacer à la fois les vitamines B₁ et B₂ dans le mélange thiamine-riboflavine-nicotinamide-adénine qui jouit du pouvoir de supprimer les manifestations neuromusculaires de l'acidose chronique.⁴ Il s'oppose également aux effets nerveux de la thyroxine.

Nous avons, d'autre part, découvert que l'acide folique est une substance de rééquilibrage qui prolonge la résistance du système nerveux aux effets excitants des déséquilibres glucidiques (au lactose ou au galactose) chez le rat ou le pigeon.⁵ Il intervient de même, en liaison avec d'autres vitamines, spécialement la vitamine K, dans le rétablissement de l'équilibre nerveux perturbé par l'introduction dans la ration de certains acides aminés: histidine, arginine et méthionine.⁶

Enfin l'acide folique qui renferme dans sa molécule de l'acide para-aminobenzoïque possède, comme ce corps et comme la biotine, l'activité vitaminique H:⁷ action préventive et curative dans les

déséquilibres alimentaires par excès d'ovalbumine, action antisulfamide décelable au niveau du système nerveux par chronaximétrie, action antagoniste du valériane de zinc, pouvoir de sensibiliser le système nerveux à la pénicilline malgré la présence de microbes pénicillino-résistants,¹ ce qui implique la possibilité d'un pouvoir sensibilisant de l'acide folique pour les microbes résistants vis-à-vis de la pénicilline.

Propriétés et indications thérapeutiques de l'acide folique semblent donc devoir être très étendues.

¹ H. Bénard, R. G. Busnel, P. Chauchard, H. Mazoué, et M. Polonovski, *C. R. Ac. Sc.* **223**, 826 (1946). ² P. Chauchard et R. Lecoq, *Ann. Biol. Clin.* **3**, 171 (1945).

³ P. Chauchard, *Rev. Scientif.* **79**, 620 (1941).

⁴ R. Lecoq, P. Chauchard, et H. Mazoué, *C. R. Soc. Biol.* **139**, 527 (1945).

⁵ P. Chauchard, H. Mazoué, et R. Lecoq, *C. R. Soc. Biol.*, 8 février 1947.

⁶ R. Lecoq, P. Chauchard, et H. Mazoué, *C. R. Soc. Biol.*, 8 mars 1947.

⁷ R. Lecoq, P. Chauchard, et H. Mazoué, *C. R. Soc. Biol.* **140**, 439 (1946).

⁸ R. Lecoq, P. Chauchard, et H. Mazoué, *Bull. Ac. Med.* **130**, 508 (1946).

MILLER, FREDERICK R. (London, Ont.). **Effects of eserine and acetylcholine on central synapses as shown by the hypoglossal nucleus and respiratory centres.**

The floor of the fourth ventricle was exposed in the cat, decerebrated with the Sherrington decerebrator. Since the hypoglossal nucleus lies immediately beneath the medullary floor it is readily accessible to the local action of acetylcholine (ACh). Respirations were recorded with the Sherrington pneumograph; tongue retractions were recorded by a crank lever connected by a thread to the tongue tip.

Eserine, 0.5 mg. intravenously, induces extra respirations and also tongue retractions, the latter slightly preceding the original respirations and occurring at the same rate. ACh. concentrations of 1.5×10^7 to $1:10^6$, applied in a rectangle (2×7 mm.) of spot test paper so as to cover the medullary floor on both sides, enhance respiratory and lingual effects; sometimes these concentrations later induce convulsive lingual contractions; at other times an ACh. concentration of 1.5×10^4 may be required to induce the lingual convulsions. Frequent deglutitions usually accompany the convulsions.

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Effects on respirations are not due to concurrent blood pressure changes, which are insignificant. Respiratory and lingual effects are abolished and also precluded by atropinization. Repeated deglutitions usually follow atropine injection. Also, after atropine, deglutition may be induced by saline on tongue base or in pharynx, thus affording further proof that the essential reflex arcs are still intact.

It is concluded that intravenous eserine and ACh. on the medullary floor stimulate the respiratory centres, probably by facilitating synaptic conduction within the centres. Eserine also induces synaptic transmission from the subjacent respiratory centres into the XII nucleus through irradiation. ACh., locally, first augments this transmission, then, in slightly greater amounts, ACh., locally, excites intensely the synapses (already eserinated) surrounding the motoneurons of the XII nucleus, thereby inducing the lingual convulsions.

The deglutitions, which often follow medullary ACh., may be caused by peripheral receptor stimulation in tongue and pharynx by the lingual convulsions; or the ACh. may be supposed to diffuse to, and stimulate, synaptic afferent endings (glossopharyngeal and vagal) within the nucleus of the *tractus solitarius*; the response would thus be comparable to the reflex deglutition induced by faradization of the inferior fovea, the currents probably stimulating adjacent afferent fibres in the *tractus solitarius* (Miller & Sherrington, *Quart. J. Exp. Physiol.*, 9, 147, 1916).

NACHMANSOHN, DAVID (New York). Effect of inhibitors of cholinesterase on conduction in nerve and muscle.

The small electric currents which propagate impulses along nerve and muscle fibers depend on the energy supplied locally by chemical reactions (the 'progressive disturbance' of *Keith Lucas*). A great variety of facts have been accumulated suggesting that the release and removal of acetylcholine are associated with the alterations occurring in the active surface membrane during the passage of the impulse. The inactivation of acetylcholine by cholinesterase, an enzyme localized in the neuronal surface and present in all conduc-

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tive mechanisms, may occur in a few millionths of a second. This speed is a prerequisite for the assumption of a correlation of a chemical reaction with electrical manifestations. The activity of this enzyme and that of cholinesterase, the enzyme which forms acetylcholine, have been correlated in several ways with the action potential.

If conduction in nerve and muscle is dependent upon the rapid removal of acetylcholine by cholinesterase, inhibitors of the enzyme should block conduction. Eserine and other anticholinesterases abolish conduction. The chemical and electrical effects are equally reversible. Di-isopropyl fluorophosphate (DFP), a highly specific and most powerful inhibitor of cholinesterase, destroys the enzyme irreversibly. This destruction is however, not an immediate process. Its rate depends on concentration, temperature, and other factors. A most striking parallelism was found between the rate of destruction of cholinesterase by DFP and the rate of abolition of conduction. This interdependence could be shown as a function of temperature as well as a function of time. The effect was demonstrated on a great variety of nerves: mammalian, cold-blooded, invertebrate, motor, sensory, cholinergic, and adrenergic, and also on striated muscle. The experiments have conclusively established that conduction and cholinesterase activity are inseparably associated.

In contrast to other anticholinesterases, prostigmine, an equally powerful enzyme inhibitor, does not affect conduction of nerve or muscle. Experiments on the giant axon of squid have revealed that prostigmine, in contrast to eserine and DFP, does not penetrate into the cell. Apparently, the conducting surfaces are surrounded by membranes impermeable for methylated quaternary ammonium salts like prostigmine, acetylcholine, and curare, except at synapses. The peculiar ability of synapses to react to certain compounds applied externally may thus be attributed to the anatomical structure rather than to a basic difference of the physico-chemical mechanism between conduction and synaptic transmission. The propagating agent in both cases is the flow of current, but in the chemical changes enabling it, release and removal of acetylcholine are necessary events.

Nachmansohn, D., *Ann. New York Acad. Sc.* **47**, 395 (1946). Bullock, T. H., Grundfest, H., Nachmansohn, D., and Rothenberg, M. A., *J. Neurophysiol.* **10**, 11 (1947).

OBRADOR, S. (Madrid). Excitability changes in cortical motor neurones induced by partial isolation.

The excitability of the motor cortex was studied in dogs with periods of five or ten seconds stimulation of condenser discharges of different frequency, duration and intensity. A frequency of 50 per second and a duration of 10 msec. for each discharge was found very adequate to elicit motor responses from the cortex. The threshold was measured by the voltage of the current.

In a series of dogs both motor areas were exposed under aseptic conditions and in one of the hemispheres the cortex was isolated by subpial circular section. An area of about 2 cm. diameter including the motor neurones was thus separated from the rest of the cortex. The main blood vessels were preserved. Both motor areas were covered with a thin piece of gutta-percha in order to avoid or diminish cortical adhesions. The animals were studied at the end of two or three months and the cortex was then exposed again for a comparative study of excitability. The partially isolated or denervated cortex responded more regularly and strongly than the side of control. The threshold was lower in the operated cortex and with higher stimuli the responses were of an epileptiform type. The local application of strychnine on both motor cortices elicited after some minutes a clonic discharge limited to the contralateral limbs of the isolated cortex. This clonic unilateral discharge was usually sustained and with regular rhythm of about 60 to 70 per minute during a long time. The cortical origin of the clonic convulsive discharge was clearly proved by the removal of the isolated cortex which suddenly stopped the discharge.

In acute experiments the isolation of the normal motor cortex with local injections of novocain also produced in one or two hours a condition of hyperexcitability for electrical stimuli and local strychnization.

These findings indicate the hyperexcitability and irritability of the cortical motor neurones following its partial isolation and represent a further example of the nervous sensitiveness or sensitization described by Cannon and others in many structures following denervation. Perhaps these phenomena play a part in the pathogenesis of some cases of epilepsy and we can suppose that an

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anatomical or functional isolation of a certain neuronal system will produce an area of hyperexcitability for different types of stimuli that may have an important role in the production of the epileptic symptoms.

OLMSTED, J. M. D. (Berkeley, Calif.). Refractive changes produced by injection of fluids into the vitreous humour.

In nembutalized cats injection of 0.2 cc. distilled water, physiological saline, or slightly hypertonic solutions of sodium chloride or sugar, all cause the same refractive change in the eye, viz. a transient hypermetropia of about 1 D. The effect is not conditioned by the tonicity of the injected fluid, nor is it the result of trauma or distortion of the shape of the globe. It can be explained on the assumption that the ciliary body behaves like erectile tissue, its volume and therefore the tension it exerts on the suspensory ligaments being altered by changes in its blood content. If stimulation of the cervical sympathetic were to cause vasoconstriction in the ciliary body, as it is claimed to do in the iris, the resulting shrinkage in its volume would increase the tension on the suspensory ligaments and produce a change in the lens in the direction of hypermetropia. The reverse would be the case on stimulation of the oculomotor if this nerve were to be found to contain vasodilator fibers to the ciliary body. Such a mechanism would supplement the direct action of radial and circular smooth muscle fibers in the ciliary body which have hitherto been considered responsible for changes in the shape of the lens during accommodation for near and far vision.

PHILLIPS, RALPH W. (Washington, D.C.). The problem of adaptability in animals and its relation to livestock improvement.

Animals differ markedly in their reactions to various environments. These differences are of major importance in determining the usefulness of domestic animals. Differences in adaptability may be observed in reproductive efficiency, growth, milk production, utilization of various types of forage, maintenance of normal body tem-

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perature and respiration rate in hot environments, and ability to withstand rigorous storms and high altitudes. Examples of variability in reproductive efficiency only will be presented here.

Average numbers of services per pregnancy in Hampshire, Shropshire, Southdown, and Karakul sheep were 2.5, 2.9, 2.9, and 1.4 respectively, at Beltsville, Maryland, over a ten-year period. Superior fertility in the Karakul probably reflects better adaptability to the hot environment that precedes the breeding season, since this breed originated where relatively high summer temperatures prevail. The mechanism of superior adaptability to such conditions is not fully understood. Ability of the scrotum to maintain testes at a low temperature may be one important factor, since the thermo-regulatory function of the tunica dartos has been demonstrated by the author and his associates. Evidence has been obtained that British breeds of sheep tend to produce semen of poor quality during the summer months, and that, within this general type, some breeds may be more affected by heat than others. Thus, the Hampshire produces semen of better quality than the Shropshire during the summer months and sexual activity is less impaired. Seasonal fluctuations have also been observed in semen and breeding efficiency of cattle. At Beltsville, Maryland, Shorthorns showed lower reproductive efficiency during June, July, and August than during other months. In Chungking, China, percentages of fertile matings during spring, summer, autumn, and winter were 51, 42, 60, and 59. Comparisons of fertility have not been made between breeds and types of cattle, but superior heat-regulating ability in *Bos indicus* as compared with *Bos taurus* cattle, and of Jerseys compared with Holsteins, indicate that differences may exist.

Average weeks of first estrus in mature sheep at Beltsville, Maryland, were: Corriedale, August 29–September 4; Karakul and Karakul × Corriedale, September 5–11; Hampshire, Shropshire, and Karakul × Blackfaced Highland, September 12–18; and Southdown, September 19–25. Termination of breeding season is more difficult to measure, but wide variations among breeds have been observed.

There is a fertile and little-touched field for physiological research in the reproductive and other aspects of adaptability in many domestic animals that contribute to human welfare.

POSTMA, N. (Utrecht). A remarkable physiological imitation of physical plasticity by the foot muscle of the snail (*Helix pomatia* L.).

Jordan's communication to the previous congress¹ gave a physical analysis of the tonic reaction (lengthening and recovery) of the hollow smooth muscles. That reaction has many properties in common with the behaviour of plastic colloids exposed to deforming forces. In the case of such substances *outward* pressure or extension is used; the muscle meets with extending forces only caused by *inner* pressure exerted by the contents of the cavity (intake of food into the gastric cavity, embryo growth in the uterus). The muscle yields as if it is undergoing a physical plastic lengthening. Just as in the model experiments (e.g. plastic rubber) there is an increase of resistance and *Jordan* interpreted that increase to be cramming ('snowplough-effect', in the case of speedy lengthening) and consolidation (in that of prolonged extension).

In the foot muscle of the snail, which possibly represents hollow smooth muscles in general, we have found that these tonic reactions are based on reflex-shortening and -distension of the muscular units. These opposite movements are effected by antagonistic impulses conducted to the muscle along efferent paths. Thus the tonic reaction is only apparently a physical one.

The keys to the recognition of this physiological imitation of a physical deformation-reaction are: firstly the discovery of tonolytic stimulation (*Postma* and *Jordan* 1942),² and secondly the establishment of the fact that after tonic contraction (tonolytic stimuli have to be prevented) the lengthening reaction was repeated only when the muscle was charged with a moderate load. When the muscle is exposed to lengthening by extension with a small load its tonus increases. Diminution of the resistance against lengthening results when the extending force is due to a large load. *Postma* and *De Jong* (1946)³ have succeeded in evoking the same effects by electrical stimulation and we can consider these reactions as tension reflexes.

The foot muscle shows besides tension-reactions caused by the extending load an increase of the tonic resistance, which originates from the lengthening itself. This is evident from the deficit in tonolytic effect if the stimulation is applied during extension: the decrease

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of tonic resistance is much greater when excitation is started before the lengthening sets in (*Postma* 1942 and 1945).^{3, 4}

These results permit us to assume the action of tonolytic and excitatory impulses even in the foot muscle and its nerve net. Consequently the reaction of the foot to tension and to lengthening may be interpreted as being due to three tonic reflexes. The reflex to lengthening and that to low tension are synergists, producing augmentation of tonus; the reflex to high tension acts tonolytically and antagonistically to the first two mentioned. We may expect a constant resistance against lengthening if the generation of tonus caused by extension is abolished by tonolytic activity of a large extending load. This type of reaction was put forward by *Jordan* as the ideal one: a constant tonus without extra demand of energy.

The question now arises whether similar lengthening reactions of the musculature of sea-anemones, of *Ascidia*, and of the hollow smooth muscles of the intestines of vertebrates are based on reflexes, identical with those described above.

¹ 'Physikalische Analyse des Tonus glatter Hohlmuskeln', *Kongressbericht* (Zürich) 3, 18 (1938).

² Postma, N., and Jordan, H. J., *Acta Brev. Néerl.* 12, 92 (1942).

³ Postma, N., *Arch. Néerl. Physiol.* 26, 426 (1942).

⁴ Postma, N., *Proc. Kon. Ned. Akad. v. Wetensch.* 46, 52 (1945).

⁵ Postma, N., and De Jong, D. J., *Acta Brev. Néerl.* 14, 15 (1946).

REHM, WARREN S. (Louisville, Ky.). The ability of the stomach to produce electrical energy.

The present work is concerned with an attempt to determine the ability of the electromotive forces of the stomach to produce electrical energy. It has been shown in previous work (*Am. J. Physiol.* 139, 1, 1942) that when the stomach potential was shunted through a low external resistance the total IR drop in the circuit was essentially equal to the open circuit voltage. On the basis of these findings a minimum value for the electrical energy output under these conditions could be calculated. It also follows from these data that the stomach can undoubtedly produce more than this amount of electrical energy. Experiments were designed to determine how much more electrical energy the stomach could produce. Non-polarizable electrodes were placed opposite each other across the stomach

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wall of amyotized dogs and a battery was connected in series with these electrodes. The positive pole of the battery was connected to the mucosal side of the stomach (the mucosal side of the stomach is normally negative in the external circuit to the serosal side) and the electrical current was measured with a milliammeter. From the laws of electrical networks, it follows that the rate of electrical energy production by the stomach under these conditions would be equal to the product of the current and the effective electromotive force of the stomach. The effective electromotive force was determined at intervals, during a period of current flow, by momentarily breaking the circuit and measuring the open circuit voltage (measured through a separate pair of non-polarizable electrodes). An attempt was made to correct these values for the effect of the capacitance of the stomach by obtaining independent values for the effective electromotive force from data obtained during the flow of current. With this method it was found that with current densities of about 0.5 milliamperes per cm.² the potential, after a temporary decrease, increased and reached a level near the original resting level. As the current densities increased the level of the potential decreased until, with currents of about 5 milliamperes per cm.², the potential was reduced to approximately zero. The rate of electrical energy output was calculated and it was found to reach a maximum when the current density was in the neighborhood of 2.5 milliamperes per cm.²

ROCHA E SILVA, M. (London). Activation of the fibrinolytic power of the blood in anaphylactic and peptone shock.

Recently,^{1, 2} we have described a technique to show fibrinolysis in blood samples taken from dogs submitted to anaphylactic and peptone shock. Since the blood becomes incoagulable because of the discharge of heparin, fibrinolysis can only be observed if the blood is made to clot by addition of a suitable dose of protamine.³ Using this technique, it was shown that fibrinolysis appears to be connected with the actual mechanism of production of those kinds of shock, since it is more pronounced after a first injection of the agent and disappears as soon as the animal becomes desensitized to further injections. The subsidence of this fibrinolytic effect 15 to 20 minutes

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after the injection of the shock-producing agent would induce one to assume that an anti-fibrinolytic substance appears in the blood. That this substance might be heparin was suspected from the beginning. We had, however, devised experimental conditions to test that possibility. Exclusion of the abdominal organs by a ligature upon the thoracic aorta and inferior vena cava just above the diaphragm ('thoracic' or anterior animal) permits an even easier observation of the fibrinolytic effect, since after the injection of peptone, the blood clots very rapidly and undergoes redissolution. This fibrinolysis appearing in the 'thoracic' animal is stronger than the one shown in the intact animal and lasts until the end of the experiment. Therefore, we can be sure that all samples taken from a 'thoracic' animal after peptone will fibrinolyse. Since heparin does not appear in those samples, we have been able to study the effect of a previous injection of heparin upon this fibrinolytic effect. Heparin injected before peptone prevented the *activation* of the fibrinolytic enzyme in the thoracic animal, but had no effect upon the *active* enzyme when added *in vitro* to the blood samples taken after the peptone injection. Therefore, heparin might be the anti-fibrinolytic factor appearing in the intact animal, but its action must be understood as a preventive one against further activation of the enzyme. The return to normal as seen in samples taken 15 to 20 minutes after the onset of the shock probably derives from a spontaneous inactivation of the enzyme by the natural inhibitor still present in the blood.

In the experiments on the thoracic dogs, pieces of the lung were taken immediately before and after the injection of peptone and smears were stained for microscopic observation, according to the technique previously described.⁴ When peptone was injected alone, platelets disappeared from peripheral blood and were found forming enormous aggregates in the lung parenchyma. Those clumps soon disintegrate completely. If heparin is injected before peptone, the platelets clumps are found well protected at the end of the experiment and no fibrinolysis occurs in the blood samples. It is, therefore, assumed that products derived from platelets might constitute the activator of the fibrinolytic enzyme in those kinds of shock.

¹ Rocha e Silva, M., and Teixeira, R. M., *Proc. Soc. Exp. Biol. and Med.* 61, 376 (1946). ⁴ Rocha e Silva, M., Andrade, S. O., and Teixeira, R. M.,

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Nature, 157, 801 (1946).³ Jaques, L. B., and Waters, E. T., *J. Physiol.* 99, 454 (1941).⁴ Rocha e Silva, M., Porto, A., and Andrade, S. O., *Arch. Surgery*, 53, 199 (1946).

SHEARD, CHARLES (Rochester, Minn.). Consideration and evaluation of the physiologic factors concerned in dark adaptation of the rods and cones in normal and clinical conditions.

Data will be presented and conclusions drawn from my recent investigations in the field of aviation medicine concerning the influence of food, metabolic rate, oxygen, age, environmental temperature, long hours of exposure to light, and various vasoconstricting and vasodilating agents on dark adaptation. With suitable physical controls and standards and a knowledge of, and regard for, various physiologic factors it is possible to obtain data repeatable from day to day to 0.1 to 0.2 log unit. Under such conditions it is possible to attempt to designate the causation of departure from the normal course and levels of dark adaptation as pigmentary, circulatory, and metabolic, or neural and cerebral. In general, vasodilating agents, such as food, are favorable to the best levels of dark adaptation, whereas vasoconstricting agents, such as smoking of cigarettes or reduction of the oxygen-carrying capacity of hemoglobin, are unfavorable. Age affects dark adaptation levels; an average difference of 0.5 log unit exists between the 10-20 and 50-60 year groups. Persons with marked nutritional disturbances, without any accompanying evidence of avitaminosis A from dermatologic or blood chemical findings and without subsequent administration of vitamin A, have shown improvement in dark adaptation due to improvement in cerebral recognition and response associated with restoration of a state of adequate nutrition and well-being.

My recent work on the values of carotene and vitamin A in blood serums (method of *Osterberg* and associates) shows that, in a group of fifty persons who had been clinically selected as evidencing some signs or symptoms of avitaminosis A, there is a 60% correlation between high threshold levels and delayed recovery of both cone and rod dark adaptation, on the one hand, and very low carotene

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(100 I.U. per 100 c.c.) and vitamin A (150-200 I.U. per 100 c.c.) levels in fasting blood serums and less than 500 I.U. per 100 c.c. six hours after the ingestion of 7,500 units of vitamin A per kilogram of body weight. The levels of cone dark adaptation are elevated 0.5 to 1.0 log unit and as much as 1.5 to 2.0 log units in the rod responses. Also, there is a definite cone knee (plateau) evidenced in the course of the dark adaptation in peripheral areas, which persists for several minutes and which is not found under identical conditions of previous light adaptation in persons with normal dark adaptation and adequate vitamin A and carotene in the blood. In certain cases there have been exhibited cone knees (plateaus) of eight to ten minutes' duration, high threshold levels of cones in the macula and, in perimetric surveys made by the technic of dark adaptation used by me, it has been possible to show marked reduction in the functioning of the rods in certain areas. Other data to be presented show that the liver plays an important role in many of these departures from normal blood findings and dark adaptation levels.

STEAD, E. A., Jr., and WARREN, J. V. (Durham, N.C.). **Mechanisms for increasing the cardiac output in man.**

The mechanisms for increasing the cardiac output above the resting level have never been studied in man. Observations on the heart lung preparation are of little help because the maximum output of these preparations does not reach the level found in the resting animal. The cardiac output was calculated from the Fick principle, the mixed venous blood being obtained by threading a catheter through the venous system into the right heart. Increasing the right atrial pressure by infusions or decreasing it by venesection or venous tourniquets had no constant effect on the cardiac output. Increasing the cardiac output by releasing arterial tourniquets applied to the extremities or by opening an arteriovenous fistula caused no rise in atrial pressure. In a large atrial septal defect the right ventricle pumps more blood than the left ventricle, but the right atrial pressure is lower than the left.

Decreasing the peripheral resistance by opening an arteriovenous fistula or by releasing arterial tourniquets causes an immediate rise

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in stroke volume which occurs in too short a time to be humoral in origin. Atropinization prevents a rise in heart rate but does not effect the change in stroke volume.

The available evidence indicates that changes in ventricular relaxation, or contraction, or both, are responsible for increasing the cardiac output under normal circumstances and that these changes in ventricular activity are not brought about mechanically by changes in atrial pressure. Both humoral and reflex mechanisms may act directly on the ventricle.

TISLOW, R., and CHESLER, A. (Bloomfield, N.J.). British anti-lewisite, protective effects in alloxan-treated rats.

BAL, in addition to preventing the diabetic effect of alloxan in rats, also reduced its lethality. The toxicity of intravenous alloxan monohydrate was reduced to half by the preceding intravenous injection of BAL.

The ED₅₀ of BAL in protecting rats against a dose of alloxan previously found to produce diabetes in all injected animals was determined.

BAL effectively prevented alloxan diabetes by both the intravenous and the subcutaneous routes. Its protection lasted from one to two hours.

TORDA, C., and WOLFF, H. G. (New York). Effect of substances decreasing acetylcholine synthesis on neuro-muscular function.

It is currently held that acetylcholine is synthesized in nerve tissue, is released at motor nerve endings, and participates in the production of the effect of indirect stimulation. It was, therefore, investigated whether decreasing acetylcholine synthesis modifies the amount of muscle contraction resulting from indirect stimulation.

The effect of various substances on acetylcholine synthesis was tested and a variety of substances were found to decrease acetylcholine synthesis. From these substances some were chosen to

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ascertain their effects on striated muscle function. All the substances had the following properties: (1) they decreased acetylcholine synthesis; and (2) they did not modify the sensitivity of striated muscle to acetylcholine. To minimize the chance that the effect observed was due to some mechanism other than decrease of acetylcholine synthesis chemically unrelated substances were used.

The sciatic nerve was stimulated for 3 seconds every 30 seconds by means of a thyatron stimulator and the amount of contraction of the gastrocnemius muscle was registered before and after the intravenous administration of the substances decreasing acetylcholine synthesis.

In all instances the muscle contraction was significantly less after the injection of the depressor agent.

The results imply that acetylcholine is important to optimal function of the nerve-muscle system.

TURMAN, W. G., and ROBB, J. S. (Syracuse, N.Y.). The conducting system in human foetal hearts and its significance in the analysis of electrocardiograms.

Reconstructions of human foetal hearts and of their conducting systems have been made in plastic. The gestation periods of the series investigated extend from 4 to 8 months. Serial sections were stained by Masson, Mallory, or the Cajal silver techniques. The atrioventricular node, main bundle, right and left branches were located in each of these hearts. The specialized tissue is readily followed because the staining characteristics are unlike those of cardiac muscle and because the connective tissue sheath is selectively stained. The differentiation of conducting tissue is progressive with the foetal age. This tissue terminates by very gradual end to end transition into ordinary muscle fibers. Each muscle cell does not receive a conducting fiber but these fibers are so numerous that very small areas of muscle are supplied by one termination. This pattern is found throughout the heart, *including the septum*.

Such an arrangement provides an almost simultaneous stimulus for polarization to contiguous areas. Although there is an anatomical syncytium within each ventricular muscle bundle, physiologically there is probably little syncytial spread within the muscle because

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contiguous areas would be active and therefore refractory at almost identical times.

Widely separated areas, for instance apex and base, would become activated at different times, because of length of conducting pathways; but the basal activation would not be as much later as one would expect if conduction had occurred mainly through muscle syncytium at the rate of 400 mm./sec.

A condition favoring onset of fibrillation develops if conduction along the pathway to one island is interrupted, or if there is local damage to the muscle cells. In either instance an island would not be refractory when contiguous areas were being depolarized. Thus it could be excited by spread of depolarization through the muscle syncytium.

Recently, electrocardiographers have suggested that depolarization of the bundle of His does not register when electrocardiograms are taken by ordinary techniques (the cross sectional area is too small, the tissue is not on the surface of the heart, and the sensitivity of the instruments used is not sufficient). If this interpretation be true, and be correlated with the anatomical description given above, then QT becomes an indication of depolarization of individual islands of ventricular muscle, a summation of activity in multiple areas. Such a theory allows explanation of the similarity of the QT waves obtained from individual muscle cells, from muscle strips, from partially developed embryo hearts, and from the very complex adult mammalian heart.

WALD, GEORGE (Cambridge, Mass.). The metamorphosis of visual systems in amphibia.

In the rods of the vertebrate retina two visual systems are found. One is based upon the red photosensitive pigment rhodopsin, engaged in a cycle with vitamin A₁; the other involves the purple photopigment, porphyropsin, bound in a similar cycle with vitamin A₂.

The porphyropsin system appears to be the more primitive in vertebrate evolution. The cyclostome, *Petromyzon marinus*, possesses only this system. The same is true of all types of freshwater fish so far examined.

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Vertebrates have followed two pathways out of fresh water, one into the sea, the other to land. Both have led them to the use of vitamin A₁ in vision. Thus all marine fishes which have been examined, with the single exception of certain *Labridea*, have the rhodopsin system alone; so also do all the birds and mammals investigated.

Interpolated between freshwater and marine fishes are euryhaline forms, which can exist as adults in either environment. Among them, the salmon and the 'freshwater' eel have mixtures of the rhodopsin and porphyropsin systems; while the alewife and white perch have only the latter. In all these forms the visual system is predominantly or exclusively that normally associated with the environment in which the fish develops embryonically, and is relatively independent of the environment in which it is found as an adult.

Interpolated between freshwater fishes and true land vertebrates are the amphibia. Their life histories for the most part are closely analogous with those of euryhaline fishes, amphibian migrations to land replacing fish migrations to the sea.

Adult frogs possess the rhodopsin system and vitamin A₁ alone. The tadpole of the common bullfrog, *Rana catesbiana*, however, just prior to metamorphosis, has exclusively the porphyropsin-vitamin A₂ system. During metamorphosis it transfers completely to the rhodopsin system, which is found alone in the newly emerged frog. Partly metamorphosed animals have mixtures of both systems, such as have been found otherwise only in euryhaline fishes.

The common newt, *Triturus viridescens*, begins its life as a gilled larva in fresh water. After several months it metamorphoses to the land-living red eft; then after 1-2 years of growth it undergoes a second metamorphosis to the sexually mature newt, returning to the water for the remainder of its life. The eye of the red eft contains a mixture of vitamins A₁ and A₂, predominantly the former; while that of the water-phase adult presents just the reverse proportions of both vitamins. This is a change opposite in direction to that in the frog, but associated in the same way with the chemical metamorphosis of visual systems.

Finally, such a permanently larval salamander as the mudpuppy (*Necturus maculosus*) contains only vitamins A₁ in its retina as an adult.

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Amphibia, therefore, like euryhaline fishes possess as a group both the rhodopsin and porphyropsin systems; but in amphibia these systems succeed one another as the animal goes through its basic metamorphoses.

WÉGRIA, RENÉ (New York). Correlation between the effect of quinidine sulfate on the rate of the circus movement in auricular fibrillation and its concentration in the blood plasma.

Patients with chronic auricular fibrillation were given orally single and repeated doses of quinidine sulfate. The concentration of the drug in the plasma and the intensity of its effect on the rate of the circus movement were followed.

In 7 studies in which one single dose (0.4 to 0.8 gm.) was given, the intensity of the cardiac effect of the drug and its plasma concentration were found to be grossly parallel but not in a strictly quantitative manner. Indeed, discrepancies between intensity of cardiac effect and plasma concentration were found, the plasma level decreasing faster than the intensity of cardiac effect.

In 3 studies in which repeated doses (0.4 gm. every 2 hours for 3 or 4 doses) were given, there seemed to be a less marked discrepancy between plasma concentration and intensity of the cardiac effect. This may be more apparent than real because the patients were not followed long enough.

As possible explanations for the discrepancies observed between the plasma quinidine level and the intensity of the cardiac effect, there are several main possibilities: (1) the plasma level, in the first few hours after the administration of the drug, is relatively higher than its auricular level because the auricles become saturated with relatively low plasma levels or because the time during which the auricles are exposed to a high plasma level is too short and, therefore, the auricles do not fix as much quinidine as might be expected from the height of the plasma level; (2) the plasma level, later in the period of action of the drug, is relatively lower than its auricular level because the auricles retain quinidine longer than the plasma; (3) the auricular level, early in the period of action of quinidine, may be

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commensurate with the plasma level but the cardiac effect is not more marked because the increment of cardiac effect tends toward zero with any further increment of the auricular level.

Experiments on dogs in which the content in quinidine of auricular and ventricular muscle was correlated with the quinidine plasma level, seem to rule out the first hypothesis as a possible explanation.

WOLF, S., and WOLFF, H. G. (New York). The function of the stomach as observed in fistulous human subjects, with special reference to the action of drugs and the effects of vagotomy.

A human subject with a gastric fistula larger than that of Alexis St. Martin was studied in detail and continuously for over five years. The effect on the stomach of a large number of drugs and chemical agents were determined on this subject, as well as on two other fistulous individuals. One of the latter was studied before and after bilateral supradiaphragmatic vagotomy.

Data obtained fell into five categories, allowing of the following inferences:

1. Secretory and motor activity in the stomach usually parallel one another and these gastric functions correspond closely to the blood flow through the organ. Drugs which inhibit gastric function induce in the stomach a state of pallor and deturgescence. Drugs which stimulate gastric activity, on the other hand, give rise to hyperemia and turgidity of the membrane.

2. The gastric mucous membrane is remarkably resistant to trauma during pallor and relative inactivity of the stomach. With hyperemia and engorgement, however, the membrane becomes far more vulnerable to physical insult, erosions and bleeding points resulting readily from minor traumata. When hyperemia and engorgement are intense and sustained, there occurs a lowering of pain threshold, so that ordinarily painless gastric contractions become painful.

3. By virtue of its protective covering of mucus, the gastric mucosa, even when red and turgid, is comparatively resistant to the action of caustic chemical agents. It was found that various drugs, including emetics commonly thought to be gastric irritants, actually

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do not exert an irritant effect on the stomach. Locally acting emetics exert their effects after passage into the duodenum.

4. Following vagotomy the stomach remained for several weeks pale and inactive. Slight hyperemia followed the ingestion of food, but situational stimuli provocative of conflict with anger and resentment and accompanied by intense gastric hyperemia before operation failed to induce such a change after the vagus innervation had been interrupted.

5. In general, the effects on the stomach of a given quantity of any drug could not be predicted without reference to the prevailing state of the organ. Gastric inhibitors, for example, whose effects were readily demonstrable when the stomach was in an average state of engorgement and activity exerted no detectable effect when the stomach was turgid and overactive. Situational stimuli provocative of emotional changes were found to be of great importance in determining the state of the stomach. The actions of the various drugs tested depended in large measure upon whether they reinforced or opposed these other influences acting at the same time.

MAY, R. M. (Paris). Régénération cérébrale provoquée par la greffe intraoculaire simultanée de tissu cérébral de nouveau-né et de nerf sciatique chez la souris.

Nous avons implanté, dans la chambre antérieure de l'œil de 132 souris adultes, du tissu cérébral de souriceau nouveau-né et, en plus, chez 87 d'entre elles un bout de nerf sciatique du même souriceau, et chez 45 autres un bout de nerf sciatique d'une souris adulte. Les yeux portegreffes ont été imprégnés à l'argent pour la plupart, depuis le 2^e jusqu'au 147^e jour après la transplantation, et coupés en séries.

Le tissu cérébral implanté a continué son développement et s'est accolé au bout de nerf sciatique greffé avec lui. Les bouts de nerfs implantés ont dégénéré comme ils l'auraient fait *in situ*. Leur dégénérescence est encore peu marquée 3 jours après leur greffe, mais ils sont en pleine désagrégation 7 jours après cette opération.

Les produits de dégénérescence et les cellules phagocytaires qui en sont chargées attirent les fibres cérébrales dont la progression peut

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être déterminée par leurs cônes ou boutons d'accroissement. L'attraction des fibres cérébrales est exercée aussi bien par des bouts de nerf de nouveau-nés que de nerf d'adultes. Les fibres attirés vers les bouts de nerfs en dégénérescence avancent vers ceux-ci isolément et en faisant souvent des trajets supplémentaires dans les tissus voisins.

Un bout de nerf de nouveau-né réhabité a, déjà 33 jours après son implantation, un aspect de nerf normal, et se distingue du tissu cérébral à fibres sinueuses et noyaux ronds par ses fibres droites et ses noyaux de Schwann allongés.

Nous avons pu observer deux connexions directes de tissu cérébral avec un bout de nerf de nouveau-né, 33 et 117 jours après leur greffe, et deux autres cas semblables avec un bout de nerf adulte, tous deux 133 jours après l'implantation. Ces connexions sont une preuve de la régénération des cellules cérébrales. Un bout de nerf adulte réhabité 133 jours après son implantation a l'aspect d'un nerf normal. Un bout de nerf de nouveau-né, étudié 127 jours après sa greffe, avait provoqué la sortie des fibres nerveuses propres de la cornée et leur pénétration dans cet implant.

Ces faits montrent qu'il est possible de provoquer la régénération des fibres de cellules cérébrales très jeunes chez la souris. Ils montrent aussi que des nerfs périphériques dégénérés, très jeunes ou adultes, exercent une action neurotrope sur les fibres de ces cellules.

HESS, W. R. (Zurich). Coordinative functions of the diencephalon.

The exploration of this subcortical region was carried out on the intact animal enjoying perfect freedom of movement. Unipolar excitation with pulsating, direct current of low frequency (8 pulsations per second) has been used as a means of recognizing the functional quality of fibers running to or running from the diencephalic coordinative center. Low frequency evokes characteristic summation from the first fiber group (or related substrata) and clear phasic responses from the second. The reactions elicited from the latter structures appear therefore unnatural, but are of analytical value. Simultaneous stimulation of two points evokes either addition or subtraction of motor effects observed, the effect depending on the

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strength of current employed. The points stimulated were usually explored with three degrees of voltage. Survival experiments after discrete coagulation have been used for the histological control of lesions and ensuing fiber degeneration. Signal-light in film marks onset of stimulation.

Interpretation:

Certain reactions have the character of compensatory motor effects, as seen under natural conditions, evoked by vestibular or proprioceptive excitation. In the experiment the animal, through artificial stimulation, is thrown out of its natural balance into an unnatural state of equilibrium, or movements of head and extremities, proprioceptive in nature, may be observed.

The automatisms observed were evoked from 'pre-diencephalic-center' structures. The rhythm of the movements is not dependent upon that of stimulation. A long latent period precedes autonomic responses. Affective reactions or changes in 'functional readiness to react' (*funktionelle Bereitschaft*) have in general prolonged after-effects, voltage, frequency, duration of stimulation playing here an important part.

ARTOM, C., and CORNATZER, W. E. (Winston-Salem, N.C.).

Action of choline and fat on the formation of phospholipides in the liver and intestine.

Previous studies have shown that lipide phosphorylation in the liver and small intestine is more active when the diet is rich in fat.¹ The present data indicate that both dietary choline and fat are involved, a finding which may be of interest in relation to a possible role of phospholipides in the absorption and metabolism of fat.

Rats were maintained for seven days on a low-fat, low-choline diet. In each experiment, four animals were given the following by stomach tube: Rat A, water; Rat B, choline HCl (30 mg.); Rat C, oil (2.2 c.c.) and choline; Rat D, oil and water. All rats were then injected with a solution of phosphate, containing radioactive P, and killed after certain time intervals (mostly six hours). On the lipides extracted from the liver and small intestine, the radioactivity and the P content were determined.

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In the intestine of Rats B, receiving choline, both the total radioactivity and the specific activity (radioactivity per mg. of lipide P) are higher than in Rats A. When, in addition to choline, fat was also given (Rats C), there was a further increase in these values. In Rats D, to which fat alone was administered, the values were usually the same as in Rats A.²

The results obtained on the liver were similar, although the differences were somewhat less consistent and not as marked as in the intestine.

The stimulation of lipide phosphorylation by a single dose of choline in the liver of rats on high-fat diet has been previously described.³ Such a stimulation has now been shown to occur in both liver and intestine.⁴ It is apparent also in rats on a low-fat diet, but it is enhanced by the simultaneous administration of a large dose of fat. This finding is in line with the results of experiments of longer duration concerning the effects of dietary choline and fat on the level of liver lecithins.⁵

¹ Artom, C., Sarzana, G., and Segrè, E., *Arch. Internat. Physiol.* 37, 245 (1938).

² In rats on adequate stock diet, the administration of oil alone does increase the radioactive values in the intestine.

³ Periman, I., and Chaikoff, I. L., *J. Biol. Chem.* 127, 211 (1939).

⁴ The administration of dimethylethanolamine, diethylethanolamine, and ethanolamine also caused an increased formation of phospholipides in the liver and intestine. The first two compounds are known to be lipotropic, whereas the last is not.

⁵ Fishman, W. H., and Artom, C., *J. Biol. Chem.* 164, 307 (1946).

**BACQ, Z. M., PATETTA, M. A., et CALDEYRO, R. (Liège).
Adrénaline dans la glande parotéide de *Bufo arenarum* après
énervation.**

L'un de nous¹ a suggéré que l'adrénaline lévogyre isolée de la sécrétion des glandes parotéides de divers crapauds tropicaux et subtropicaux² est en réalité de la sympathine qui s'accumule et dont l'oxydation est inhibée par la haute teneur de cette sécrétion en acide ascorbique et en glutathion réduit. Nous essayons de vérifier cette hypothèse en étudiant les modifications apportées par l'énervation unilatérale de la parotéide de *Bufo arenarum* H.

On vérifie histologiquement la disparition des fibres nerveuses (vraisemblablement sympathiques postganglionnaires) dix jours après brossage du pédicule à l'acide phénique 5%; à ce moment les granulations donnant, dans les cellules glandulaires, les réactions histochimiques des phénols sont beaucoup plus abondantes dans la glande énnervée que dans la glande normale,³ cependant que la teneur en adrénaline de la sécrétion diminue. Ces faits montrent que cette glande concentre facilement les phénols après énnervation (ce qui pourrait expliquer l'hypersensibilité à l'adrénaline des tissus énnervés), mais synthétise plus difficilement l'adrénaline.

¹ Bacq, Z. M., *Ergebnisse d. Physiol.* 37, 156 (1935). ² Voir littérature dans Gessner, O., *Handb. exper. Pharmak. Ergänzungswerk*, VI band, Springer, Berlin, 1938, p. 47. ³ Patetta, M. A., *Arch. Soc. Biol. Montevideo*, 12, 291 (1945).

BARCLAY, J. A., COOKE, W. T., and KENNEY, R. A. (Birmingham). Evidence for a three-component system of renal excretion.

The excretion of any urinary constituent may be regulated by (a) filtration at the glomerulus, (b) reabsorption in the tubules, (c) secretion into the tubular urine. It has not previously been suggested that there may be a combination of all three. A study of the excretion at various plasma levels, either by a direct comparison of the clearance of the substance under investigation with that of the reference substance used to measure glomerular filtration rate (inulin, mannitol, or creatinine) or by calculation of the index E

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(Barclay and Kenney, 1946),¹ makes it possible to decide which combination of these excretory processes is involved.

We have shown that phosphate in the dog (Barclay, Cooke, and Kenney, 1946)² may be secreted by the renal tubules when the plasma level be elevated sufficiently, and that this substance has a definite secretory 'Tm'.

The figures given by Ekehorn (1945)³ and Shannon (1936, 1938)⁷ for urea excretion give evidence of the participation of secretion in addition to filtration and reabsorption at elevated plasma levels. We have been able to demonstrate the secretion of urea in a number (12) of hypertensive and nephritic patients even when the plasma levels were within normal physiological limits.

Potassium which is normally reabsorbed to a great extent from the glomerular filtrate may under certain conditions have a clearance equal to, or exceeding, that of inulin (Nunn, 1929;⁶ McCance and Widdowson, 1937;⁵ Keith and Osterberg, 1940).⁴

Many members of the sulphonamide group of compounds (e.g. acetyl-sulphathiazole) provide examples of the simultaneous occurrence of tubular reabsorption and secretion. In such a case the presence of the secretory component may be recognised by the self-depression of clearance when the plasma level be elevated beyond the value required to saturate the tubule cells.

That such widely differing entities as urea, the phosphate ion, the potassium ion, and the sulphonamides should be excreted by a three component system suggests that this process may occur under normal physiological conditions. The advantages of the possession of such a combination of excretory mechanisms to the body are great. Filtration at the glomerulus provides a fluid from which the renal tubules can absorb solutes and water and into which secretion can occur. The final concentration of any urinary constituent can thus be regulated very precisely by alterations in the balance of the two tubular processes. Indeed, the high diffusibility of certain of the urinary constituents, notably urea, would make secretion essential to explain the concentration of these substances found in the urine.

¹ Barclay, J. A., and Kenney, R. A., *Acta Medica Scand.* 125, 386 (1946).

² Barclay, J. A., Cooke, W. T., and Kenney, R. A., Oral Communication to the Physiological Society, April 1946.

³ Ekehorn, G., *Acta Medica Scand.*

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- 122, 134 (1945). ⁴ Keith, N. H., and Osterberg, A. E., *Am. J. Physiol.* 129, 395 (1940). ⁵ McCance, R. A., and Widdowson, E. M., *Lancet*, 2, 247 (1937). ⁶ Nunn, M., *Skand. Archiv. f. Physiologie*, 55, 211 (1929). ⁷ Shannon, J. A., *Am. J. Physiol.* 117, 206 (1936); 122, 782 (1938).

BARNES, T. CUNLIFFE (Philadelphia, Pa.). **Electrical action of acetylcholine.**

The distinction between cholinergic and adrenergic nerves can be represented in an oil-cell model containing triglyceride oil which produces electrical phase-boundary potentials with sympathomimetic drugs but not with acetylcholine (Barnes and Beutner, *Science*, 104, 569, 1946; *Nature*, in press). 20 c.c. of triacetin after shaking with 100 c.c. of H₂O had a resistance of 50×10^8 ohms, after shaking with saline the resistance was 40×10^8 ohms, after shaking with 0.01 M acetylcholine in saline the resistance was 40×10^8 ohms, but after shaking with 0.01 M pargoline in saline the resistance fell to 20×10^8 ohms. The function of choline esterase in adrenergic nerves is obscure, but the electrical effect of true choline esterase in brain can be shown in a model. Five grams of ground rabbit cortex in 0.9% NaCl (with chloroform as bacteriostatic) containing 100 mg.% bicarbonate reduced the electrical phase-boundary potential of 25 mg.% acetyl-beta-methylcholine from 30 mv. negativity to 14 mv. negativity. One mg.% eserine or 0.05% di-isopropyl fluorophosphate preserves the electrogenic action of acetylcholine solutions in presence of serum esterase. Nachmansohn (*J. Neurophysiol.* 9, 9, 1946) found that anti-esterase agents did not arrest the descent of the spike in nerve, suggesting that esterase plays no part in impulse formation.

One milligram of acetylcholine released at a saline-guaiacol interface produces a phase-boundary wave of negativity of several millivolts lasting 0.1 to 0.3 of a second as recorded by an electroencephalograph. This experiment suggests the possibility that a few gamma of acetylcholine formed at the lipid layer in nerve might produce a wave of negativity.

On frog sciatic in isotonic glucose 1 in 700,000 acetylcholine produces 8 mv. negative phase-boundary potential. The same concentration added to a different length of the same nerve in a second dish with the second electrode reduced the potential difference between the electrodes to zero (model of propagation).

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Addition of one milligram of carbamylcholine to the exposed cat's cortex increased frequency of the E.E.G. (Sjöstrand effect) which helps to explain Darrow's finding (*J. Neurophysiol.* 7, 217, 1944) that stimulation of the petrosal nerve increases frequency of E.E.G. Slow E.E.G. activity in the alkalosis of hyperventilation might result from hydrolysis of acetylcholine. Excess E.E.G. activity in grand mal is believed to result from excess acetylcholine whilst the slow waves in petit mal suggest deficiency of acetylcholine (Williams, *Lancet*, 240, 476, 1941).

The writer wishes to express his thanks to Dr. R. Beutner for helpful advice.

BISSAR, F., and KRUEGER, H. (Beirut, Lebanon). **Frog temperature and survival at low pressures.**

During January and February 1947, the stomach temperature varied between 14.0 and 18.0 (average 16.6°) for frogs maintained in air in small wire baskets for one hour at room temperatures between 15 and 19.5° C. The frog temperatures were sometimes slightly above and sometimes slightly below that of the room. The average weight loss per hour of these frogs was 0.71 gm. with a S.D. of 0.44 gm. A total of sixty frogs were subjected for 5, 10, 15, 30, 45, and 120 minutes to pressures between 10 and 20 mm. Hg. Their average temperatures immediately after evacuation were respectively 14.7, 10.7, 10.8, 7.4, 7.2, and 8.5° C. with a general standard deviation of 0.5° C. Corresponding average weight losses were 0.44, 0.51, 0.55, 1.30, 2.38, and 3.28 gm. during the entire evacuation period, or at average rates of 5.28, 3.06, 2.20, 2.60, 3.17, and 1.64 gm. per hour. The average rate of weight losses per hour for the first three 15-minute periods were calculated to be 2.20, 3.00, and 4.32 gm. per hour and for the last 45-minute period 0.72 gm. per hour. Temperatures decreased 5.8, 3.4, and 0.2° C. during the first three 15-minute periods and then increased 1.3° C. during the next 45 minutes. The interpretation of these figures is complicated by variability in the size of the frogs, humidity and temperature of the room, and the reaction of the frogs within the evacuation jar. The data clearly indicate that there is a rapid drop in temperature to a low level of 7.2° C. in 45 minutes and subsequently an increase to 8.5°.

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The loss of 1 gram of water at 10°C . is equivalent to 590 calories. During the first 5 minutes the average weight loss of 0.44 gm. would correspond to a heat loss of 260 calories or around 8 calories per gram of frog. As the temperature dropped only 2.3°C . the frog either developed heat or received heat from his environment. As long as the water loss was rapid the temperature of the frog would continue to drop; but when the loss and the body temperature were low, the heating effect from the environment presumably could be sufficient to cause the frog temperature to rise, even though the water loss of 0.72 gm. per hour is equivalent to a heat loss of 425 calories per hour, or about 14 calories per hour per gram of frog.

All frogs survived for more than 10 days after being subjected to evacuation periods up to 1 hour. Only 3 of 15 frogs survived a 2-hour evacuation.

BRUN, GEORG C. (Copenhagen). Rhythmic variations in the diameter of arteries in rats.

Experiments were carried out on adult white rats anesthetized with urethane. The animal was placed in a rectangular container with Ringer's solution at a temperature of 38°C . so that only the head remained above the solution. Arteries in the mesentery and in the muscles of the abdominal wall were observed through a Leitz 'ultrapak' microscope with direct objective illumination. Measurements of the diameter of the vessels were made by means of a screwing ocular micrometer.

The mesenteric arteries displayed small but distinctly visible rhythmic contractions at a rate of about 10-20 per minute. When adrenaline in small doses was squirted into the Ringer solution just above the site of measuring, a strong contraction ensued followed by a phase of dilatation in which the rhythmic contractions became very pronounced. Application of adrenaline to the artery 10-15 mm. proximally to the site of measuring caused no initial contraction, but about $\frac{1}{2}$ minute later the rhythmic contractions became very strong. Ephedrine applied direct elicited the same strong rhythmic contractions.

Anesthetizing of the arteries with nupercaine did not eliminate

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the effect. When the blood-pressure was as low as 40 mm. or when the artery was compressed proximally to the site of measuring, locally applied adrenaline would elicit a normal contraction of the artery, but no succeeding rhythmical contractions. No connexion was found between normal blood-pressure variations or respiratory movements and the rhythmic diameter variations.

In the arteries of striated muscles the rhythmical contractions were more conspicuous, but less frequent, on an average only 6 per minute. Two and 12 contractions per minute, respectively, were found in two arteries only about 2 cm. apart from each other. Small amounts of adrenaline applied locally increased the strength and frequency of the rhythmic contractions. Unlike what was found in the mesenteric arteries, anesthetizing suspended for a while the rhythmical activity without affecting the sensibility to adrenaline. Local application of ephedrine, though causing the arteries to contract, likewise suppressed the rhythmic contractions.

The experiments indicate a structural difference between the mesenteric arteries and the arteries of the striated muscles. The rhythmic activity of the mesenteric arteries seems to be a property of the plain muscles of the arterial wall, whereas the rhythmic contractions of the muscle arteries are elicited through the arterial nerves. An adequate blood-pressure level is a necessary condition that this phenomenon may occur.

CAPRARO, V., MILLA, E., e PASARGIKLIAN, M. (Milano).
Über den Metabolismus der Aceton-Körper.¹

Bekannterweise ist es nötig einen bestimmten Mindestwert des Verhältnisses zwischen verbrauchten Fetten und Kohhydraten nicht zu überschreiten, damit eine vollkommene Verbrennung der Fettsäuren stattfindet; wenn dieses Verhältnis unter diesen Mindestwert sinkt (das heißt unter 3:3/1, und den entsprechenden R.Q. = 0.77), erscheint eine Anhäufung und eine vermehrte Ausscheidung der Aceton-Körper, welche als Zwischenprodukte des Fettsäurenmetabolismus angesehen werden (Ketose).

Shaffer erklärt diese Erscheinung durch die Annahme, daß die Verbrennung der Aceton-Körper mit dem gleichzeitig stattfindenden

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den Karbohydratenmetabolismus in irgendeiner chemischen Weise verbunden ist (ketolytische Wirkung der Karbohydrate). Dieselbe Erscheinung wird aber auch auf andere Weise erklärt, indem man annimmt, daß in einigen Tierarten und im Menschen, die Fettsäuren oxydation nicht den ganzen energetischen Bedarf decken kann, weil der Organismus nicht im Stande ist, ein Intensitätsmaximum in der Fettsäuren oxydation zu überschreiten; aus diesem Grunde, wenn diese Grenze überschritten ist, muß der Karbohydratenmetabolismus aufs Neue zunehmen, sonst werden die Fettsäuren unvollkommen verbrannt und es erscheint die Ketose (antiketogene Wirkung der Karbohydrate).

Letztere Anschauung ist für uns glaubwürdiger aus folgenden Gründen:

1. Wenn die Shaffersche Annahme richtig wäre, müßte die Geschwindigkeit, mit welcher die in großen Quantitäten eingeführten Aceton-Körper aus dem Blute eines nicht Karbohydrate verbrauchenden Organismus (z. B. eines pankreasektomierten Hundes) verschwinden, niedriger sein, als jene im Falle eines Karbohydrate verbrauchenden Organismus (z. B. eines mit gemischter Kost ernährten Hundes); aber *dies ist nicht der Fall*.

2. Wenn die Shaffersche Annahme richtig wäre, müßten die Ketose und die Aceton-Körper-Ausscheidung gleichzeitig mit dem Metabolismus zunehmen, so daß der Organismus, welcher Fette und Karbohydrate in einem konstanten Verhältnis, unter dem Werte 3:3/1, verbraucht, vom Grundumsatz zu einem mehrfach größeren Metabolismus übergeht; aber *nicht nur ist dies nicht der Fall*, sondern die Aceton-Körper-Ausscheidung *nimmt mit der Zunahme des Metabolismus ab*, was bedeutet, daß die Fähigkeit die Aceton-Körper zu verbrennen mehr als der Metabolismus zunimmt.

3. Schließlich wenn die Shaffersche Annahme richtig wäre, müßten die Ketose und die Aceton-Körper-Ausscheidung sofort abnehmen, wenn der Fettsäurenmetabolismus plötzlich abnimmt wegen einer hervorgerufenen Zunahme des Karbohydratenmetabolismus, während der gesamte Energieumsatz unverändert bleibt (z. B. nach Insulin-Einspritzung); auch *trifft nicht dies zu*, im Gegenteil beobachtet man unter diesen Bedingungen *statt einer Abnahme eine vorübergehende Zunahme* der Aceton-Körper-Ausscheidung.

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Dieses unvorhergesehene Verhalten der Ketose in den drei obigen Fällen läßt sich, unserer Meinung nach, nur erklären, wenn man den Aceton-Körpermetabolismus als chemisch unabhängig von dem Kohhydratenmetabolismus, vielmehr nur von dem Gleichgewicht zwischen Aceton-Körperproduktion (Fettsäureoxydation) und Aceton-Körperoxydation, abhängig annimmt.

¹ Die Arbeiten, aus welchen die obige Mitteilung zusammengefaßt ist, sind folgende: Capraro V., e E. Milla, *Arch. di Sc. Biol.* 27, 451 (1941). Capraro V., e E. Milla, *ibid.* 30, 53 (1944). Capraro V., e M. Pasargiklian, *ibid.* 30 (1944-5).

CATCHPOLE, HUBERT R. (Chicago, Ill.). **Cellular distribution of glycoprotein in the anterior pituitary gland.**

By the use of the Hotchkiss technique of visualizing polysaccharide or polysaccharide complexes, a carbohydrate material was demonstrable under certain conditions in cells of the anterior pituitary gland. In view of the glycoprotein nature of pituitary gonadotrophic hormones, it seemed desirable to study glands in various stages in which changes in hormonal activity have been directly demonstrated or inferred. Pituitary glands were taken from adult female rats during the oestrus cycle, pregnancy, and following castration, from normal and castrated adult male rats, and from female rabbits before and after mating. Preliminary studies showed a glycoprotein material to be associated with granules of castration cells in the highest amounts seen. During the rat cycle, the amount of specific material was highest in the interval and fell progressively during pro-oestrus, oestrus, and post-oestrus. The solubility characteristics of the material seen in castration cells was compatible with a tentative identification with pituitary gonadotrophic hormone. The varying amounts of this material seen during the rat cycle agrees with direct determinations of gonadotrophic activity made by other authors in the pig and the rabbit.

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CHAKRABARTY, M. L. (Calcutta, India). On the blood-sugar in human starvation cases : 1. During the period of starvation.

Studies on hypoglycaemia have since revealed that it is possible for an individual to live practically without any symptoms with a blood-sugar varying from 21 to 37 mg. per 100 c.c. and symptoms may appear when the level comes down to 14 to 18 mg.¹ Similar records are not few, but in spite of this, the present subject has its great importance not merely because low blood-sugar is not accompanied with hypoglycaemic symptoms but because the study was on the human beings about whom not much information is on record.

This paper presents a short note of an investigation on 407 individuals selected from 9,765 starvation cases admitted in to hospital during the Bengal famine of 1943-5. Only those cases were selected who showed clinically no disease, confirmed later on from autopsy, where possible. They had profound emaciation and a few could hardly talk.

In this investigation ordinary blood constituents showed great deviation from normal but only blood-sugar forms the subject matter in this paper. Blood was collected from a vein before the individual had anything by mouth or intravenously and examination started within 15 minutes (method of *Wu and Folin*) with all usual precautions.

Table 1

Blood-sugar in mg. per 100 c.c.				
Below 80			80-120	above 120
Below 40	40	Above 40		
% 5.6	% 3.9 59.1	% 90.5	% 34.7	% 6.2

The range varied from 19.2 to 307 mg. per 100 c.c. with an average of 76.7 mg.

One case with cancrum oris showed a blood-sugar of 17.6 mg. per 100 c.c. This case has been published separately.²

It will be seen that nearly 60% had blood-sugar below the lowest normal, of which again 5.6% is below 40 mg. per 100 c.c.

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Sugar tolerance (50 gm. glucose orally) showed (1) low initial sugar, (2) gradual rise for nearly 4 hours, and (3) little tendency for the sugar level to decline, unlike a normal individual where the highest rise occurs within one hour and the level comes down within two hours.

Stained microsection (haematoxylin and eosin) after death showed (1) extensive epithelial denudation and submucous haemorrhage in the small intestine; (2) shrinking and interference with the staining of the liver cells with wider intercellular spaces; and (3) fewer cells in the islets of Langerhans and also foamy cells.

These findings afford adequate evidence for the slow absorption of sugar and their delayed disposal.

¹ Conn, J. W., *Journal of American Medical Association*, **115**, 1669-75, (1940). ² Chakrabarty, M. L., *Jour. Ind. Med. Assoc.* **14** (1945).

CHAKRABARTY, M. L. (Calcutta, India). On the blood-sugar in human starvation cases: 2. During the period of recovery.

The sugar tolerance curve in the previous communication showed that at a particular stage of starvation, absorption and utilisation of sugar are considerably hampered. Post-mortem findings showed that not only the absorbing surface but also the organs responsible for storage were damaged.

During the period of recovery, sugar tolerance tests (same method) done every two weeks showed the reverse, i.e. (1) gradual elevation of the fasting blood-sugar level, (2) time for highest rise approaching the first hour, and (3) blood-sugar gradually reaching the initial level within two hours. These changes in blood sugar ran parallel to changes in other constituents; thus the plasma protein-ratio which showed a reversal during starvation, albumen reaching the lowest 1.333% and globulin the maximum 4.54%, returned almost to normal. The recovery, of course, required more than two months when put on to good diet.

From this it is obvious that the organs which suffered damage during starvation as evidenced by the already described post mortem findings, gained gradual repair to a considerable extent within this period.

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The question that arises now is how it was possible for the individuals to remain alive with such low blood-sugar.

The investigation shows that not only life was compatible but it was possible even without any hypoglycaemic symptoms.

Everybody knows that in starvation the body passes through a series of changes, which are too well known, but in the present case, the adjustment it attained at a stage just before death, seems to be a very interesting one. The adjustment comprised maximum reduction in the expenditure of body material for energy, even at the cost of the body tissue as seen in the broken intestine and other organs. (Liver of protein-starved rats showed a similar picture.)¹ In addition the heart and respiration slowed down. The individuals could execute no muscular movement, even uttering a word. Their oxidation process came down as well and the little oxygen that could be carried by 1.74 gm. haemoglobin per 100 c.c. (*Hellige's* method) (lowest in this series) was found adequate for life process. This is how the system struggled for existence and verily it was possible only because it was a chronic starvation. In acute starvation death ushers in earlier.

¹ Campbell, R. M., and Kosterlitz, H. W., *Proc. Physiol. Soc. J. Physiol.*, 106 (1947).

COLE, H. H., and CASADY, R. B. (Davis, Calif.). Studies relating to prolificacy in rats.

This study comprises a physiological comparison of two strains of inbred rats differing significantly in prolificacy—a gray strain having an average litter size of 8.9 and a white strain with an average of 6.5. Both strains are highly inbred as the result of brother-sister or sire-daughter matings for 13 or 14 generations. The two inbred strains derive from a common ancestry involving a sire-daughter mating.

The objects of the study were twofold: to determine if indices of prolificacy could be developed; to ascertain the cause of the difference in prolificacy of the two strains.

Indices of prolificacy: The average age at sexual maturity for 25 gray females was 36.0 days, for 20 white females 41.7 days. The difference is highly significant ($t = 6.6$ and $P < 0.01$). The more

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prolific strain matures earlier and thus conceivably age at sexual maturity may serve as an index of prolificacy.

A direct relationship exists between ovarian weight and prolificacy. At 27 days of age, the average ovarian weight for 26 gray females was 17.9 mg. as compared to 10.4 mg. for 22 white females ($t = 11.2$ and $P < 0.01$). Thus it appears that ovarian weight may likewise be used as an index of prolificacy.

Cause of the difference in prolificacy of the two strains. A difference in the rate of gonadotrophin secretion was suspected, but our data on the gonadotrophic potency of the pituitaries of the two strains do not support this view. Immature rats were implanted with 5 pituitaries per rat from sexually mature females over a 5-day period. Eight recipients receiving pituitaries from gray donors had an average ovarian weight of 57.9 mg.; 7 recipients receiving implants from white donors 61.8 mg. Since potency of a gland and secretory rate are not always correlated, it is still possible that greater gonadotrophin secretion in the gray females accounts for the greater prolificacy.

The gray strain has larger thyroids. Expressing thyroid weight in mg. per 100 gm. body weight, the thyroids of the white strain at 85 to 90 days of age weigh 9.71 mg., the thyroids of the gray strain 11.3 mg. ($t = 4.158$ and $P < 0.01$). The means of the absolute weights are 19.0 and 24.4 mg. respectively. Possibly, differences in thyroid activity may account in part for the difference in prolificacy.

COURNAND, A. (New York). **Influence of intermittent positive pressure breathing upon cardiac output and intracardiac pressures in man.**

Intermittent positive pressure breathing (IPP.) was studied in 29 human subjects with essentially normal circulation. The pressure was increased in the thorax during inspiration by means of automatic respirators producing different kinds of mask pressure curves. Cardiac output was determined by the direct *Fick* method (Cournand, *Fed. Proc.* 4, 207, 1945) with the subject supine and in a fasting state. Control cardiac outputs were determined at ambient pressure before and after the IPP. Simultaneous pressure tracings were recorded

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from the right heart, peripheral artery and face mask. Intrapleural pressures were recorded in 5 cases with therapeutic pneumothorax. Net end diastolic pressures in the right ventricle could then be calculated from each beat in these cases. Mean mask pressure was determined by planimetric integration. Three types of IPP. mask curves were compared: (i) symmetrical with gradual increasing and decreasing slope, expiratory time approximately the same as inspiratory and minimal expiratory pressure above atmospheric; (ii) asymmetrical with rapidly increasing pressure during inspiration and rapidly dropping during expiration, long inspiratory and short expiratory time intervals and minimal expiratory pressure above atmospheric, and (iii) asymmetrical with gradually increasing pressure during inspiration and suddenly dropping early in expiration to atmospheric and expiratory time equal to or exceeding inspiratory. The results obtained are summarized in the table.

Type of mask pressure curve	(i)	(ii)	(iii)
Number of experiments	16	10	7
Mean mask pressure, mm.Hg.	7.0	10.6	5.7
Percent change in cardiac output	-14.5	-16.5	6.0

Correlation between height of mean mask pressure and decrease in cardiac output was good in (i) and (ii); but did not apply to (iii), as no decrease occurred in any case. With all types of mask pressure curves, the net end diastole pressures were lower during period of increasing intrapleural pressures with IPP. than during ambient breathing. The reverse occurred during the period of decreasing intrapleural pressure when the curves showed an early rapid drop of pressure. Interpreted in terms of variations in stroke volume, these changes suggest that the deficit incurred during the phase of increased intra-pleural pressure, is compensated for during the phase of decreasing intra-pleural pressure, when it is of sufficient duration and when the pressure rapidly reaches atmospheric.

V. EULER, U. S. (Stockholm). Preparation and biological properties of sympathin.

Extracts of various mammalian organs contain a sympathomimetic substance in relatively large quantities, having the chemical properties of a catechol compound but differing from adrenaline in the

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following respects, when blood-pressure equivalent doses were compared: (1) weaker inhibition of non-pregnant cat's uterus; (2) weaker dilatation of cat's pupil; (3) pressor action less readily inhibited and not reversed by ergotamine; (4) fluorescence reaction absent or weak.¹⁻³

The active substance agreed in these respects with catechol-ethanolamine or noradrenaline (arterenol). The relation of activity to strength of catechol reaction supports the assumption of identity.

A quantitative study of the distribution of the substance in various tissues and organs showed the highest amounts in the sympathetic trunk (30-100 μ g. adrenaline pressor equivalents per gm.) and in other nerves rich in adrenergic fibres, such as the splenic nerves (20 μ g./gm.), the splanchnic and carotid nerves. Grey sympathetic rami contained much more activity than the white ones. The substance was also found in cutaneous sensory nerves, motor nerves (mixed), vagus nerve, and, to a small degree, in spinal roots.

The presence of the sympathomimetic substance in organ extracts corresponded to some 10 μ g. adrenaline pressor equivalents per gm. in the spleen of various animals, and approximately 5 μ g. per gm. in heart, liver, and skeletal muscle. Normal human blood contained some 4 μ g. noradrenaline equivalent per 100 ml.⁴ Low activity was found in brain tissue and no activity in placental extracts. This distribution suggested that the activity was connected to the adrenergic nerves, which was also supported by degeneration experiments. It is therefore probable that the active principle is identical with the adrenergic transmitter in the organs concerned (sympathin). This is supported by the recent findings of Gaddum and Goodwin⁵ who found that liver sympathin released *in vivo* by stimulation of the hepatic nerves closely resembled noradrenaline in its actions. The belief of some authors that adrenaline is first liberated at the nerve endings and then transformed into sympathin is not substantiated by our experiments.

The amount of sympathin in the extract of whole spleen as compared with that in the periarterial splenic nerves seems to indicate a higher content in the finer ramifications and possibly the nerve endings of the adrenergic nerves.

The active substance is soluble in ether in the presence of lecithine or cephaline and could be eluted with water from such solution,

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suggesting a reversible linkage between sympathin and nerve lipids which might be of physiological significance.

¹⁻³ Euler, U. S. v., *Acta Physiol. Scand.* 11, 168 (1946); *J. Physiol.* 105, 38 (1946); *Acta Physiol. Scand.* 12, 73 (1946). ⁴ Euler, U. S. v., and Schmitter-löw, C., *Acta Physiol. Scand.* 13 (1947). ⁵ Gaddum, J. H., and Goodwin, L. G., *J. Physiol.* 105, 357 (1947).

FLEXNER, L. B., COWIE, D. B., and VOSBURGH, G. J. (Washington, D.C., and Baltimore, Md.). **Studies of vascular permeability with radioactive and stable isotopes.**

In our investigations on the permeability of the placenta, it has been necessary to follow the decrease with time of the concentration in the blood plasma of intravenously injected radioactive and stable isotopes. In the guinea pig's plasma, the time-concentration data of deuterium oxide and radiosodium were fitted by a single exponential from which the rate of exchange of the sodium and water of the plasma with that of the extracellular fluids could readily be determined. It was found that 60% of the sodium and 146% of the water of the plasma escaped to the extravascular fluid per minute.^{1,2} The vascular wall, consequently, was judged to be about 2.5 times as permeable to water as to sodium.

Similar measurements have recently been made with chlorine (in collaboration with *W. S. Wilde*) and iron each tagged with one of its radioactive isotopes. Although analysis of the chloride data is not yet complete, it appears that 128% of the chloride of the plasma is exchanged with extravascular chloride per minute and that the permeability of the vascular wall to chloride lies between that to water and sodium. Preliminary experiments with iron indicate that its rate of exchange is of an entirely different order and that only about one-half of the plasma iron is exchanged per hour. This low rate is attributed to the state of iron in the plasma where it is present as the alpha-globulinate.

It is our purpose to estimate the permeability of the vascular wall to other substances tagged with their isotopes in an endeavor better to understand the nature of the vascular wall and to permit comparison of its behaviour with that of other membranes being similarly studied in this and other laboratories.

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¹ Flexner, L. B., Gellhorn, A., and Merrell, M., *J. Biol. Chem.* 144, 35 (1942).

² Merrell, M., Gellhorn, A., and Flexner, L. B., *J. Biol. Chem.* 153, 83 (1944).

FONTAINE, M., et CALLAMAND, O. (Paris). Sur l'activité anti-gonadotrope du sérum d'anguille.

Si des travaux antérieurs ont mis en lumière diverses propriétés du sérum d'anguille vis-à-vis des mammifères (action toxique, hémolytique, modification du tonus et de la perméabilité des vaisseaux), il ne semble pas que son intense activité antigonadotrope (A.G.) ait été jusqu'à présent signalée. Nous l'avons mise en évidence et principalement étudiée dans le sérum d'anguille argentée femelle, injecté à de jeunes souris impubères, immédiatement avant que celles-ci reçoivent des injections d'hormone gonadotrope. Selon leur sexe et la nature de l'hormone employée (gonadostimuline A, ou A et B) la réponse était testée d'après les réactions vaginales, utérines, ovariennes ou des vésicules séminales.

Nous ne pouvions espérer déceler cette action A.G. que si celle-ci se manifestait encore à des dilutions ne présentant plus d'action toxique, ou si un chauffage ménagé pouvait annihiler la toxicité en laissant subsister une activité A.G. C'est bien ce qu'a révélé l'expérience. Quelques essais effectués avec des sérums de carpe, injectés aux mêmes doses que les sérums d'anguille n'ont révélé que de légères actions, tantôt frénatrices, tantôt accélératrices, nullement comparables à celles, inhibitrices, observées avec le sérum d'anguille. Il s'agit donc là d'une propriété qui n'est pas commune à toutes les espèces de téléostéens et qui varie d'ailleurs d'intensité chez l'anguille, selon son état physiologique et son milieu.

L'action toxique et l'action A.G. du sérum d'anguille sont-elles attribuables à la même fraction sérique? Après avoir constaté que la substance A.G. n'était pas ultrafiltrable, nous avons effectué par diverses méthodes, chimiques et physiques, la séparation de certaines fractions protéiques du sérum. Les essais effectués, à égalité de teneur en azote, nous ont montré que ce pouvoir A.G. était essentiellement localisé dans les globulines. Si la conclusion de Mosso pouvait être conservée, à savoir que la toxicité du sérum d'anguille est supportée par sa fraction albuminique, la démonstration serait faite de la nature différente des protéines toxiques et antigonado-

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tropes. Mais nos expériences actuelles au cours desquelles les globulines révèlent une toxicité beaucoup plus marquée que celles des albumines, ne permettent pas une telle conclusion. Il semble bien que les fractions les plus toxiques et douées de la plus grande activité A.G. soient toutes deux comprises dans les globulines précipitant pour des concentrations salines faibles et présentant des vitesses de migrations lentes, c'est-à-dire dans les fractions connues chez les mammifères sous l'expression de γ globulines.

Des fractionnements plus poussés pourront seuls établir si les globulines toxiques et antigonadotropes sont identiques ou seulement de constitution voisine.

• HARPER, A. A., and RAPER, H. S. (Manchester). **Pancreozymin.**

It has been shown in acute experiments in cats that the administration of meals results in an increased output of enzymes in the pancreatic juice even in animals in which all the extrinsic nerves have been cut (*Harper and Vass, 1941*).⁴ Since secretin has no stimulant effect on enzyme secretion, it seemed likely therefore that there existed in the intestinal mucosa a second hormone capable of stimulating enzyme production. *Harper and Raper (1943)*¹ extracted this substance, pancreozymin, from the intestinal mucosa of pigs, and separated it from secretin.

The method of preparation involves the extraction of the secretin and pancreozymin in alcohol. The secretin is precipitated by the addition of bile salts, and the pancreozymin is then precipitated from the supernatant liquid by saturation with NaCl. Subsequent work has shown that commercial bile salt preparations vary very much in their efficiency as precipitants of secretin, and to achieve complete separation of secretin and pancreozymin a mixture of pig and ox bile salts is required.

Pancreozymin may also be separated from secretin in acid extracts of intestinal mucosa. Enterogastrone is prepared by the method of *Hands, Greengard, Preston, Fauley, and Ivy (1942)*.¹ The pancreozymin it contains is removed by precipitation with 75% alcohol (by volume) at definite pH, the secretin remaining in solution. The precipitate yields up its pancreozymin, leaving some inert insoluble material, by extraction with 50% alcohol (by volume) at 37° C.

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Pancreozymin is thermostable, dialyses slowly through cellophane, is stable in acid but not in alkaline solution, and, when prepared by the second method described, is destroyed by peptic digestion and by pancreatic juice. These characteristics suggest that pancreozymin, like secretin, may be a protease.

Pancreozymin stimulates the production of amylase, trypsinogen, and lipase by the pancreas without, in the cat, causing any flow of juice. Pancreozymin has no vasodepressor effects, and its activity is unaffected by atropine. The increased output of enzymes in response to repeated injections of pancreozymin is maintained for periods of 3 or 4 hours. In contrast to the effect of secretin, which does not alter the histological picture of the pancreas, prolonged pancreozymin stimulation, like prolonged vagal stimulation, markedly depletes the enzyme granules in the acinar cells. (Harper and Mackay, 1945.)¹

¹ Hands, A. P., Greengard, H., Preston, F. W., Fauley, G. B., and Ivy, A. C., *Endocrinology*, **30**, 905 (1942). ² Harper, A. A., and Mackay, I. F. S., *J. Physiol.* **104**, 27 p (1945). ³ Harper, A. A., and Raper, H. S., *J. Physiol.* **102**, 115 (1943). ⁴ Harper, A. A., and Vass, C. C. N., *J. Physiol.* **99**, 415 (1941).

HARRELL, GEORGE T. (Winston-Salem, N.C.). Changes in capillary permeability as related to circulatory failure in infectious diseases.

Peripheral circulatory failure probably occurs in many infectious diseases. We have observed two types of circulatory collapse in certain acute conditions, such as meningococcemia, with and without bilateral adrenal cortical hemorrhage (Waterhouse-Friderichsen syndrome). The administration of adrenal cortical hormone, along with accepted measures for support of the circulation, will effect improvement in cases with adrenal cortical hemorrhage, but its administration is not necessary in peripheral circulatory collapse without adrenal hemorrhage. The absence of edema in both these types of collapse suggests that capillary permeability is probably of less importance in these cases than is loss of capillary tone.

We have shown that in acute infections of longer duration, such as Rocky Mountain spotted fever, peripheral circulatory failure is accompanied by a decrease in serum proteins and the development

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of generalized edema. The drop in serum proteins is preceded by an increase in the excretion of urinary nitrogen, and can be partially alleviated by a very high-protein diet.

It seems likely that in this disease capillary permeability is altered so that protein, electrolytes, and water escape into the interstitial spaces. Accordingly, in more recent investigations serial determinations of the blood volume and 'extravascular thiocyanate space' were done at intervals during the course of the disease and were compared with the levels of serum protein and with the intake and output of fluid. The blood volume was found to drop simultaneously with an increase in thiocyanate space; the alteration in the thiocyanate space is greater than that in the blood volume, however.

Similar alterations in the blood volume and thiocyanate space have been observed in patients with serum sickness, and have also been reproduced experimentally in rabbits with serum sickness. Thus it would appear that an allergic mechanism may be responsible for the alteration of capillary permeability, although allergy in rickettsial diseases has not yet been demonstrated. Preliminary experiments in rabbits with trichinosis, an infection which is known to produce a high degree of allergy, tend to confirm this thesis.

These concepts of the mechanism of circulatory collapse are probably applicable to many infectious diseases. They suggest that in cases where there is no involvement of the adrenal cortex, proper replacement of protein and the avoidance of excessive administration of crystalloids should help to prevent circulatory and respiratory failure.

VAN HARREVELD, A. (Pasadena, Calif.). Effects of asphyxiation and narcotics on the polarization state of central nervous tissue.

Gerard (1930)¹ and recently *Wright* (1947)² found that an asphyxiated part of a peripheral nerve becomes negative with respect to an oxygenated portion. It was assumed that this is due to the depolarization of the asphyxiated part, causing a potential difference between this and the oxygenated and thus polarized portion of the nerve. This potential difference is comparable with the nerve injury poten-

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tial. Since the oxygen requirements of the nerve cells are higher than those of the nerve fibers (Holmes, 1930),³ it is likely that, when the entire neuron is asphyxiated, depolarization sets in more speedily in the nerve cell than in the fiber. We thus must expect that asphyxiation of central nervous tissue will cause a potential difference between the depolarized cells and the still polarized fibers, which will disappear again when the nerve fibers also depolarize. It has been found that these asphyxial 'depolarization potentials' can be led off from the spinal cord, using an active electrode in the gray matter and an indifferent electrode on a root. The latent period of this phenomenon depends on the method of asphyxiation: after stopping the respiration the potential developed after an average of 52 seconds, after clamping the aorta immediately under the diaphragm after an average of 8.5 seconds. These differences are explained by the difference in oxygen reserve available to the nerve cell with these two methods of asphyxiation. The depolarization potential is promptly and completely reversible after asphyxiations up to about 15 minutes. The depolarization potential can be considered as an indicator of the polarization state of the nerve cell.

The administration of ether in a preparation in which the polarization state of the nerve cell had been tested by short asphyxiations, did not cause consistent potential differences between gray matter and root. However, when after etherization the polarization state was tested again, it was found that the depolarization potential was smaller or even absent, indicating a depolarization of the nerve cell. Since etherization itself did not cause a consistent galvanometer deflection, this can be explained only by the assumption that ether depolarizes the cells and fibers equally and uniformly. Pentobarbital (nembutal) has a similar action.

Whereas the depolarization caused by asphyxiation is clearly related with the oxygen requirements of the nervous elements, this is not the case with the depolarization caused by narcotics. The latter may be due to a direct action of these drugs on the polarized membrane.

¹ Gerard, R. W., *Am. J. Physiol.* 92, 498 (1930). ² Wright, E. B., *Am. J. Physiol.* 148, 174 (1947). ³ Holmes, E. G., *Biochem. J.* 24, 914 (1930).

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HARRIS, G. W. (Cambridge). **The secretory product of the neuro-hypophysis and the excitation of the adeno-hypophysis.**

The hypothalamo-hypophyseal region of the conscious rabbit has been stimulated electrically by the remote control method. A coil (2,000 turns) was implanted beneath the scalp with an insulated lead passing through a small trephine hole in the skull to the desired region. Stimulation was performed by placing the animal's head in an electro-magnetic field. Spread of stimulus was not more than $\frac{1}{2}$ mm. for fibres in the hypophyseal stalk. Experiments demonstrate (1) that the secretory product of the neuro-hypophysis elicited by stimulation has relatively less pressor and anti-diuretic activity (compared with oxytocic) than standard posterior lobe extracts, and (2) that stimuli applied to various regions produce varying amounts of gonadotropic secretion. The results of the latter experiments appear to confirm neuro-vascular transmission of stimuli from the hypothalamus to the adeno-hypophysis via the hypophyseal portal vessels.

HARTMAN, F. A., BROWNELL, K. A., THATCHER, J. S., and GLASS, C. (Columbus, Ohio). **A new adrenal hormone.**

The movement of fat from the reserves to the liver during inanition depends upon the adrenal cortex, since it fails to occur if the latter is destroyed. The substance responsible, which we propose to call the 'fat factor', has been separated from the sodium and carbohydrate factors by chromatographic adsorption. It causes deposition of fat in the liver of an adrenalectomized animal during starvation, while the other factors do not. Likewise, the crystalline compounds corticosterone, 11-dehydrocorticosterone and 11-dehydro-17-hydroxycorticosterone, are unable to do this. Further evidence that the carbohydrate and fat factors are distinct has been obtained from animals whose adrenals have been enucleated. The output of these factors reaches a point above normal one or more weeks after enucleation. However, the maximum increase for the fat and carbohydrate factors develops at widely different times.

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Preliminary work indicates that the fat factor causes a significant reduction in metabolism. If injected every 6 hours for 48 hours, this effect persists for 2 or 3 weeks.

HAUROWITZ, FELIX (Istanbul). The structure of the protein molecule.

While there is no doubt about the peptide structure of the protein molecules, no satisfactory answer has yet been given to the question as to whether or not the peptide chains are ramified. Side chains might branch off from cystine molecules or from the second carboxyl groups of aspartic or glutamic acid. Both modes of ramification would result in the presence of more than one terminal α -carboxyl group per protein molecule. Such groups form thiohydantoin derivatives, when heated with ammonium thiocyanide and acetic anhydride (*Schlack and Kumpf, 1926*), while the free carboxyl groups of aspartic and glutamic acid cannot undergo this reaction. The treatment of casein, edestin, zein, and globin with thiocyanide and acetic anhydride leads to an increase of the sulphur percentage by approximately 0.5%. A part of this sulphur could be extracted by boiling benzene, while another part remained bound to the proteins. It was found that thiohydantoins give a green colour with aquoferricyanide and an attempt was made to determine the amount of thiohydantoin groups colorimetrically. The experiments indicate that the peptide chain of the protein molecules is only weakly ramified.

HECHT, S., LAMAR, E. S., SHLAER, S., and HENDLEY, C. D. (New York). Size, shape, and contrast in the detection of targets by daylight vision.

Measurements have been made of the brightness contrast required for the detection of rectangular targets brighter than their background at 2,950 foot lamberts, corresponding to sunlit sand, water, and sky, and at 17.5 foot lamberts corresponding to the ambient brightness shortly after sunset. The targets varied in area between

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0.5 and 800 square minutes, and differed in the ratio of length to width between 2 and 200.

For the detection of targets both of whose dimensions are less than 2 minutes, the total flux added to the background by the target is constant; contrast varies inversely with area and the product of the two is constant. For targets whose dimensions are greater than 2 minutes more flux is required as the area increases until for large targets above 200 square minutes the required contrast becomes independent of area.

For areas below 100 square minutes, square targets are most efficient for their area. The greater the ratio of length to width in a target the more flux does it require for detection.

It appears that the visually critical region of the target is the ribbon just inside its perimeter and about 1 minute wide. Contrast is therefore judged not over an area, but across its boundary. These measurements were made by a frequency-of-seeing method. They may be described quantitatively by probability considerations derived from the quantum nature of light and the mosaic structure of the retina. For a target to be seen against a background, one or more cones in the visually critical region inside the perimeter of the retinal image must each absorb at least 4 light quanta in addition to what they absorb from the background. This number of required additional quanta is independent of background brightness, and even at the highest brightness is above the random fluctuations or 'noise level' of the background.

HODGKIN, A. L. (Cambridge). **The local electric changes associated with repetitive action in a single nerve fibre.**

Fessard,¹ *Arvanitaki*,² and others have shown that crustacean nerve readily gives rise to repetitive discharges when stimulated with weak constant currents. Isolated axons from *Carcinus Maenas* behave in a similar manner, provided that reasonable care has been taken with the dissection and that the experimental animals are in good physiological condition. The characteristics of the discharge vary considerably from axon to axon (cf. *Fessard*,¹ *Erlanger*, and *Blair*³) and it is convenient to divide the preparations into the following classes:

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1. Axons in which the recovery cycle shows no significant supernormal phase and which are capable of repetition over a wide range of frequencies. In such axons the frequency varies smoothly with the applied current over a range of about 10-100 impulses per second.

2. Axons with a pronounced supernormal phase. This class usually gives a train of impulses of frequency 50 to 100 per second which is only slightly affected by the applied current.

3. Axons with high threshold and low safety factor which do not repeat unless the current strength is much greater than rheobase. Axons in this class tend to have low membrane resistance.

About 50% of axons fall into the first class and their behaviour has been analysed with a view to answering the following question. What is the nature of the process which enables an axon with a spike duration of 1 m.sec. and a refractory period of less than 10 m.sec. to repeat stably at a frequency of 10/sec.? As Fessard¹ has suggested the response time is an important factor. The maximum response time is often as great as 100 m.sec. and may last for nearly one second in exceptional cases.

Electrical recording of the potential changes at the stimulating electrode shows that the following sequence of events occurs when a constant current is suddenly applied. First the membrane charges to a value determined by the membrane resistance with a time constant of 5 to 10 m.sec. Upon this charging process is superimposed a slow creep of potential which may be regarded as an actively generated local response. When the potential at the cathode reaches a certain value a propagated action potential results. With weak currents it may take over 0.5 sec. for the local response to reach propagating strength. During activity the membrane is discharged and the whole process must be repeated before a second spike can arise. There is therefore a striking resemblance between the potential changes which precede the first impulse and those which precede any other impulse in the repetitive train.

¹ Fessard, A., *Propriétés rythmiques de la matière vivante* (1936). Paris, Hermann & Cie.

² Arvanitaki, A., *Les Variations graduées de la polarisation des systèmes excitable* (1938). Paris, Hermann & Cie.

³ Erlanger, J.,

and Blair, E. A., *Am. J. Physiol.* 114, 328 (1935).

HODGKIN, A. L., and HUXLEY, A. F. (Cambridge). Potassium leakage and absorption by an active nerve fibre.

*Osterhout*¹ and *Blinks*² have shown that potassium ions have a specific effect in raising the membrane conductance in *Nitella*. *Côlé* and *Marmont*³ have obtained similar results in the squid axon. In *Carcinus* axons the membrane conductance is increased by a factor of about three when the potassium content of sea-water is raised from its normal value of 10 mm. to one of 30 mm. An isolated axon which has been immersed in oil is surrounded by a shell of sea-water which is only about three μ in thickness. The membrane conductance should therefore change markedly when a train of impulses passes along an axon if there is any appreciable leakage of potassium during activity. We have found that the membrane conductance was increased to three or four times its normal value at the end of a 1 minute tetanus of frequency 50 per sec. After activity had ceased the membrane conductance returned smoothly to its normal value with a half time of a few minutes. The recovery of conductance could be greatly accelerated by washing the axon with normal sea-water. It was also shown that activity had only a slight cumulative effect on membrane conductance when the axon was immersed in a large volume of sea-water. These results indicate first, that activity was associated with the leakage of a substance which affected membrane conductance in the same way as potassium ions; and second, that the potassium-like substance was re-absorbed during the period of recovery.

The increase in the concentration of the potassium-like substance was roughly proportional to the number of impulses transmitted provided that the duration of activity did not exceed 30-60 seconds. The concentration appeared to reach a steady level after a few minutes when activity was maintained for a long time.

The evidence for identifying the unknown substance with potassium is as follows. Both unknown substance and potassium carried similar increases in membrane conductance and both had relatively little effect on membrane capacity. Both were absorbed by the axis cylinder at rates of comparable order of magnitude. Further, *Cowan*⁴ and *A. C. Young*⁵ have shown chemically that activity causes an appreciable leakage of potassium in non-medullated nerve. The

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unknown substance cannot be acetyl choline, since this was found to have no significant effect on membrane conductance.

The quantity of potassium lost by an axon was calculated on the assumption that the effects observed were due to potassium leakage. An average value of 1.7×10^{-12} was obtained for the number of moles which leak through 1 square centimetre of membrane during one impulse. The charge carried by this number of moles was roughly twice that carried by the resting membrane.

- ¹ Osterhout, W. J. V., *Biol. Rev.* 6, 367 (1931). ² Blinks, L. R., *J. Gen. Physiol.* 13, 495 (1929). ³ Cole, K. S., and Marmont, G., *Fed. Proc.* 2, 1, 15 (1942). ⁴ Cowan, S. L., *Proc. Roy. Soc. B.* 115, 216 (1934).
⁵ Young, A. C., *J. Neurophysiol.* 1, 4 (1938).

HOFFMAN, M. M. (Montreal). Metabolism of progesterone.

The metabolism of the hormone of the corpus luteum has been studied in the rabbit. It has been shown that this species converts administered progesterone to pregnanediol-3(α), 20(α) glucuronide. The amount of pregnanediol excreted in the urine accounts for less than 20% of the progesterone administered. No other metabolite could be isolated, nor could the faeces be shown to contain an appreciable amount of pregnanediol. The fate of the remainder of the administered progesterone is as yet unknown. The conversion of progesterone to pregnanediol has been demonstrated to occur in the absence of the uterus, ovary, testis and adrenal. The role of the liver and vitamin E in the metabolism of progesterone will be discussed.

KLEIBER, MAX (Davis, Calif.). Metabolic rate of starving rats and their tissues *in vitro*.

Rats starved at an environmental temperature varying between 18 and 28° C. survived on the average 9 days. The mean survival time at 20° C. was 12 days, at 30° C. 17 days, and at 35° C. 16 days. At an environmental temperature of 38° C. the rats died during the first day.

The total weight loss during starvation, in per cent. of the original

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body weight, amounted to 29% for rats starved at 18 to 28° C., 36% for those starved at 20° C., 41% for those starved at 30° C., and 40% for those starved at 35° C.

The metabolic level (metabolic rate per unit of the $\frac{1}{2}$ power of body weight) of the starving rats was expressed in per cent. of the basal metabolic level measured in preliminary trials at 30° C. after a 16 hour fast at 30° C. This relative metabolic level (in per cent. of the basal level) on the day before death, amounted to 73% for the rats starved at 18 to 28° C. but measured at 30° C. It amounted to 112% for rats starved and measured at 20° C., to 46% for rats starved and measured at 30° C., and to 56% for rats starved and measured at 35° C.

The rate of oxygen consumption *in vitro* of excised tissues from rats starved from 4 to 16 days was considerably lower than the *in vitro* metabolic rate of corresponding tissues from rats fasted only 16 hours. This decrease of tissue metabolism by starvation amounted to 30% for diaphragm, 50% for brain cortex, and 60% for liver slices.

This result confirms earlier observations on the correlation between metabolic rate of tissues *in vivo* and *in vitro*. The major factors directly controlling metabolic rate in the living animal apparently are carried over with the excised tissues to the micro-respiration chamber.

KRUEGER, HUGO (Beirut, Lebanon). Morphine, ileal peristalsis, and distending pressures.

Subcutaneous injection of morphine in doses of 0.5 mg. per kilogram usually initiates peristalsis in Thirty-Villa loops of the ileum in dogs. Activity of the lower ileum in such preparations was recorded once weekly, for periods of 200', from a Brodie bellows connected to a tandem, double-chambered, water-filled balloon inserted into the lumen of the loop. During each experiment the pressure remained constant, but from week to week pressures of 5, 10, 15-80 or 85 cm. of water were used to distend the chambers of the balloon. Morphine was administered after a 100' control period. Peristalsis was noted after the morphine at all pressures studied.

It must be emphasized in favor of Bayliss and Starling and against

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Alvarez that preceding a peristaltic wave there is a clear-cut quiescent period of longer than 10 seconds associated with 84% of the waves. Further, at all pressures the relaxation of the ileal muscles (as indicated by the filling of the chambers of the balloon) was greatest just prior to the expulsion of water from the balloon by the wave advancing caudad. *Thus undoubted inhibition usually precedes the wave of contraction.*

The velocities of the caudally progressing peristaltic waves were 9-14 mm. per second at 5 and 10 cm. of water and dropped to 4-7 mm. per second at 55-75 cm. pressure. The peristaltic waves usually cleared 90% or more of the water from the balloon up to 50 cm. pressure, but at higher pressures emptying was incomplete and only 57% clearance was obtained at 85 cm. of water pressure. With decreasing clearance the velocity of the waves increased to reach values of 14-20 mm. per second at 85 cm. pressure.

The volume of water present in the balloon chambers and hence the volume generally displaced by the peristaltic wave increased with the pressure. The work done per wave in displacing water from the posterior chamber increased from 45 gram cm. in 9" at 5 cm. pressure to 1,200 gram cm. in 10" at 75 cm. pressure. Thus the rate of work increased from 5 gram cm. per second to 120 gram cm. per second. At 85 cm. the work done was only 900 gram cm. in 13" or 70 gram cm. per second.

Peristaltic waves are thus capable of moving water effectively against pressures as high as 70 cm. of water, but against greater distending pressures only partial closure of the lumen is obtained.

LAPICQUE, LOUIS, et LAPICQUE, MARCELLE (Paris). *Théorie chronaxique de l'inhibition de Setchenow.*

La donnée classique que le mésencéphale exerce une inhibition sur le pouvoir réflexe de la moelle a été formulée par *Setchenow* à la suite d'expériences indiscutables sur le réflexe de *Turck* (retrait d'une patte plongée dans un acide); elle fut généralisée par lui-même dans un raisonnement sommaire. Or nos études quantitatives sur le réflexe par stimulation électrique d'un nerf centripète montrent au contraire que le réflexe est moins facile après ablation de l'encéphale;

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c'est alors qu'il prend chez la grenouille le caractère itératif. La divergence diamétrale entre ces deux séries de résultats correspond à une considérable différence chronaxique entre les voies centripètes dans l'un et l'autre cas. Les fibres nerveuses que mettent en jeu nos stimulations électriques sont des plus rapides (chronaxies de l'ordre du dix-millième de seconde); les fibres mises en jeu par l'application d'acide sur la peau sont parmi les plus lentes (*Adrian*, puis *Zotterman*).

Nos recherches antérieures et celles de nos collaborateurs nous permettent de poser ceci: 1° L'excitation passe d'un élément à un autre d'autant plus facilement que les chronaxies sont plus voisines. 2° La nécessité de la sommation pour l'obtention du réflexe électrique sur la grenouille spinale s'explique en admettant entre le nerf centripète rapide et le nerf moteur rapide l'interposition d'un neurone internuncial à chronaxie plus grande. 3° Le mésencéphale abaisse la chronaxie de certains neurones médullaires (*Marcelle Lapicque*, 1923). 4° Sur la grenouille entière, si la sommation n'est pas nécessaire, c'est que le mésencéphale supprime ou diminue l'hétérochronisme qui constituait une résistance dans l'arc réflexe médullaire (*D. Acevedo*, 1930, *H. Schriever*, 1932).

Appliquant ces données au réflexe chimique avec ses fibres centripètes à grandes chronaxies, on voit au contraire que cette même action du mésencéphale, abaissement du neurone internuncial, doit créer ou augmenter un hétérochronisme formant obstacle.

L'explication est théoriquement satisfaisante. Voici deux faits qui l'appuient.

1° La subordination des extenseurs, identifiée depuis longtemps, et pour d'autres raisons, au mécanisme abaissant la chronaxie des neurones internunciaux, diminue ou disparaît sous toutes les influences physiologiques ou pharmacologiques qui favorisent le réflexe aux acides.

2° Après ablation du mésencéphale, une petite quantité de strychnine, dont l'effet spécifique est d'abaisser les chronaxies nerveuses, diminue ou même arrête le réflexe aux acides.

LEHR, DAVID (New York). The prevention of renal damage by the use of mixtures of sulfonamides.

Solubility studies were performed in water and in normal human urine with various combinations of sulfanilamide (SA), sulfapyridine (SP), sulfathiazole (ST), sulfadiazine (SD), sulfamerazine (SMD), sulfamethazine (SMMD), sulfapyrazine (SPZ), and sulfacetimide (SAC), as well as their acetylated homologues. It was found that several sulfonamides, even if closely related, can be dissolved simultaneously in the same solvent to the full extent of their separate saturation levels without the occurrence of precipitation. Based on this observation the toxicity, the absorption and excretion, the antibacterial activity and the therapeutic effectiveness of sulfonamide mixtures, were investigated.

In the experimental animal, the toxicity of the combinations ST-SD, SD-SMD, ST-SD-SMD, SD-SP, SD-ST-SP, SD-SMD-SPZ and SD-SMD-SAC, was strikingly low if compared with the toxic effect of equal or comparable total dosages of any one of the N_1 -heterocyclic derivatives of sulfanilamide. Evidence derived from post-mortem examinations and from chemical analyses of the blood, kidneys, and urine, proved that the low toxicity of mixtures was due to a significant decrease or absence of intratubular deposition of sulfonamide crystals in the kidneys and thus to the prevention of renal obstruction.^{1, 2}

Mixtures of sulfonamides were more completely absorbed and excreted than equal amounts of their individual constituents, since the body handles each sulfonamide as if it were present alone and in the amount contained in the mixture. Blood and urine levels from such combinations, were, therefore, distinctly higher than expected on the basis of mathematical computations from the values of single compounds in full dosage.

The antibacterial effect of sulfonamide mixtures, tested *in vitro*, was essentially additive. In some instances, combinations proved distinctly more active than one or several of their individual components at equal concentrations.

On the basis of these experimental observations, the clinical use of sulfonamide mixtures was expected to result in a significantly smaller incidence of renal complications without decrease in the antibacterial

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efficacy. A group of 600 unselected patients with acute systemic infections was treated, under carefully controlled conditions, with a SD-ST combination (equal amounts) using the routine oral dosage (in adults, 4 gram of the mixture initially, 1 gram every 4 hours; in children 0.1-0.2 gram per kilogram body weight in 24 hours). Therapeutic results were uniformly satisfactory and were conspicuous in many instances because of the speed of clinical improvement or cure. Effective blood levels of sulfonamide and high drug concentrations in the urine were readily maintained. Crystalluria was infrequent, despite the intentional omission of adjuvant alkali therapy. No signs of renal irritation were encountered.^{1,4} Similar results were obtained with the clinical administration of a SD-SMD combination using both the oral and subcutaneous route. This study is continuing at present.

The clinical observations with combinations of two sulfonamides and the results of animal experimental studies indicate that the use of a mixture containing three sulfonamides in human therapy would almost completely eliminate the possibility of concretum formation in the urinary tract at the routine dose level. Hence, it would also obviate the necessity for adjuvant alkali therapy.

It is suggested that the simultaneous employment of two or three sulfonamides in partial dosages should replace the use of single compounds, since mixtures combine a high therapeutic efficacy with a significantly lowered renal toxicity. Confirmation of these experimental and clinical results have recently come from several sources.^{1,6,7}

¹ Lehr, D., 'Inhibition of drug precipitation in the urinary tract by the use of sulfonamide mixtures. I. Sulfathiazole-sulfadiazine mixture', *Proc. Soc. Exper. Biol. and Med.* **58**, 11 (1945).

² Lehr, D., 'The toxicity of sulfonamide mixtures. II. Combinations of sulfathiazole, sulfadiazine and sulfamerazine', *ibid.*, under publication.

³ Lehr, D., 'The prevention of renal complications by the therapeutic employment of sulfonamide mixtures. I. Sulfathiazole-sulfadiazine combination', *J. Urol.* **55**, 548 (1946).

⁴ Lehr, D., Slobody, L. B., and Greenberg, W. B., 'The use of a sulfadiazine-sulfathiazole mixture in the treatment of children', *J. Pediat.* **29**, 275 (1946).

⁵ Flippin, H. F., and Reinhold, J. G., 'An evaluation of sulfonamide mixtures and various adjuvants for control of sulfonamide crystalluria', *Ann. Int. Med.* **25**, 433 (1946).

⁶ Whitehead, R., *Sect. Exper. and Therap.*, A.M.A. Meeting, San Francisco, 3 July 1946.

⁷ Frisk, A. R., Hagerman, G., Helander, S., and Sjogren, B., 'Sulfacombination', a new principle of chemotherapeutic treatment', *Nord. Med.* **29**, 639 (1946).

LIPSCHITZ, WERNER L. (Pearl River, N.Y.). Regulation of the kidney functions in various species of animals.

Urinary excretion was studied in rats, dogs, and healthy persons. To determine diuretic effects they were brought to a low excretion rate by complete fasting or feeding of only saline solution. Anti-diuretic effects were studied on animals either hydrated previously by tap-water or in the stage of diuresis produced by diuretics, e.g. formoguanamine. The diuretic action of drugs is in proportion to the dose. The useful diuretic dose range of formoguanamine is 2.5 to 10 mg./kg. in the rat, 7.5 to 15 mg./kg. in the dog, and 4.5 to 9 mg./kg. in man. Diuretics and the antidiuretic hormone are active in dogs and rats independently of whether the kidneys are innervated or denervated. The action of the xanthine diuretics is irregular in rats, dogs, humans, and even rabbits.

On the other hand, there are examples in which the kind of kidney response is dependent upon the species of animals. Hydrated dogs as well as rats react to morphine with antidiuresis but on the basis of different mechanisms. In the *dog* with innervated or denervated kidneys, morphine is supposed to act via a depression of nervous centres, release of acetylcholine and by this (*Verney, Pickford, de Bodo*) stimulation of the production of the antidiuretic hormone. Amounts of 9 to 28 m.u./kg./hr. of hormone were found in the urine of dogs injected subcutaneously with 5 mg./kg. morphine. In the urine of *rats* injected with 20 mg./kg. morphine only traces to 3 m.u./kg./hr. of the hormone were found, and, as *Gibbs and Fulghum* found, in contrast to the effect of pitressin, the output of chlorides was not increased. When the kidneys were decapsulated and denervated morphine had almost no antidiuretic effect, although pitressin was fully effective. Evidently the renal nerves play a much more important role in the rat than in the dog. Morphine also counteracts diuresis produced by diuretics, whereas the antidiuretic hormone or phenobarbital are ineffective under the same conditions. Here again kidney denervation in the *rat* prevents the morphine effect. In the *dog* kidney denervation or the administration of desoxycorticosterone is without influence upon the morphine antidiuresis. Therefore a third mechanism seems to be active involving either the anterior lobe of the hypophysis or the kidney itself.

LOUBATIÈRES, A. (Montpellier). Analyse du rôle de l'insuline dans le processus de glycogénoformation hépatique provoqué par l'administration d'extrait total de lobe antérieur d'hypophyse.

Nos expériences précisent les conditions dans lesquelles l'administration d'extrait frais total d'antéhypophyse accroît ou diminue le taux du glycogène existant dans le foie. Elles portent sur le *chien normal* en post-absorption digestive, 16 heures après le repas, ou soumis préalablement à un jeûne de 2 à 8 jours, et sur le *chien dépancréaté* traité ou non par l'insuline.

Les prélèvements de foie (500 milligrammes) ont été effectués sous brève anesthésie étherée, à l'aide du bistouri électrique, et les dosages de glycogène faits en double ont donné par leur moyenne le résultat retenu.

C'est sur l'animal *éveillé* entre les prélèvements de tissus et se comportant normalement que l'extrait antéhypophysaire a été amené à agir (dose: 1 centimètre cube par kilog. et par jour par voie sous-cutanée; 1 centimètre cube représentant 1 gramme de lobe antérieur).

Nos conclusions sont les suivantes:

Chez le *chien normal soumis à un jeûne de 2 à 8 jours*, l'extrait détermine en 4 jours l'accumulation de glycogène (accroissement de 310 % en moyenne). Le poids du foie augmente (50 % en moyenne). Il en résulte que le stock global hépatique s'élève d'une façon considérable. Cette accumulation remarquable de glycogène se produit malgré la prolongation du jeûne et sans modifications appréciables de la glycémie.

Chez le *chien normal en post-absorption digestive*, l'extrait détermine en 4 jours, soit le maintien du taux glycogénique initial, soit des variations légères qui peuvent se produire dans les deux sens. Le poids du foie s'accroît en moyenne de 80 %. Le stock total hépatique se trouve donc accru également dans ces conditions.

Dans ces deux types d'expériences, le taux du glycogène musculaire diminue toujours.

L'extrait anté-hypophysaire administré au *chien dépancréaté privé d'insuline depuis 5 jours*, mais récemment alimenté, ne possède pas d'effet glycogénoformateur sur le foie. Le taux de 0,11 % trouvé en

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moyenne, est inférieur à celui habituellement admis chez l'animal témoin privé de pancréas (0,2 %).

L'insuline injectée en même temps que l'extrait de lobe antérieur permet l'accumulation de glycogène dans le foie du chien dépancréaté. L'ampleur du phénomène est fonction du degré de compensation exercé par l'insuline sur l'état diabétique consécutif à la dépancréatation et aggravé par l'extrait diabétogène d'antéhypophyse.

Si les doses d'insuline sont insuffisantes pour ramener la glycémie à la normale, le taux du glycogène hépatique demeure bas (0,3 %). Par contre, si le diabète est bien maîtrisé, des taux voisins de ceux observés chez l'animal normal sont trouvés (3 %).

L'insuline joue donc un rôle prépondérant dans la manifestation glycogénoformatrice qu'exerce sur le foie de l'animal normal, l'administration d'extrait total de lobe antérieur d'hypophyse.

Loubatières, A., *J. Physiol. et Path. Gén.* 38, n° 1, 71-84 (1941-3). *Tra-*
vau des Membres de la Soc. Chim. Biol. 25, 1404-8 (1943).

MCDOWALL, R. J. S., MIECHOWSKI, W., and SHAFEE, A. Z.
(London). **The release of a muscle sensitizing substance from stimulated nerve.**

The rat diaphragm preparation of *Bülbring* offers a convenient method of studying neuro-muscular transmission. The following points have so far been ascertained:

1. If a small strip of diaphragm is placed in the same small bath with two phrenic diaphragm preparations, stimulation of the nerves of these two preparations brings about a sensitization of the test strip to direct stimuli, although there may be little or no change in its tone. The test strip becomes sensitive to strengths of stimuli not previously effective.

2. The release of the sensitizing substance occurs after curare and with rates of stimulation which do not cause the muscle to contract.

3. For the above experiments, eserine is necessary and stimulation of the nerves may bring about in the test strip typical eserine twitches not previously present.

4. Repeated stimulation and washing which liberate apparently all the available sensitizing substance, do not affect the responses

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to slow nerve stimulation or produce fatigue, but the well-known potentiating effect of tetanus is absent.

Many of the above results suggest that the sensitizing substance is acetylcholine, but since the addition of this substance to the bath does not give corresponding results, the subject is being investigated further.

MUUS, JYTTE (South Hadley, Mass.). Observations on an increase in lymph clotting time following thermal burns.

The observation that lymph from a burned area has a decreased tendency to coagulate was made accidentally during a series of experiments where such lymph was collected for chemical analyses. (Glenn, Muus, and Drinker, *J. Clin. Inv.* **22**, 451, 1943; Muus and Hardenbergh, *J. Biol. Chem.* **152**, 1, 1944; Muus, Hardenbergh, and Drinker, *Am. J. Physiol.* **142**, 284, 1944.) Glenn, Peterson, and Drinker had previously shown that the amount of swelling in a burned area depended on the degree of coagulation of the exudate (*Surgery*, **12**, 685, 1942).

Most of the experiments were performed on calves under nembutal anesthesia scalded by immersion of one or both front legs in boiling water. Lymph was collected by cannulating a lymphatic in the shoulder which drains most of the lymph from the leg. Normal clotting time was somewhat irregular but varied usually between 6 minutes and 12 minutes. Immediately after the burn it increased to several hours and sometimes the lymph completely lost its ability to coagulate spontaneously. If small amounts of thromboplastin (a crude extract from lung) were added, the lymph clotted immediately.

Determination of fibrinogen showed that it was slightly higher than in normal lymph. Prothrombin times according to Quick (*J.A.M.A.* **110**, 1658, 1938) were unchanged or slightly shorter than normal. The presence of an anticoagulant therefore seemed the most plausible explanation. This was verified by adding lymph to oxalated normal plasma and determining the clotting time after recalcification. The clotting time of the mixtures of plasma and burned lymph was greater than that of either plasma and normal lymph or plasma and saline. This showed that the increase in clotting time was not a simple effect of dilution of the plasma, and

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indicates that an anticoagulant is present. The anticoagulant does not seem to be heparin because addition of small amounts of protamine (Jacques and Waters, *J. Physiol.* 99, 454, 1941) has no effect. Neither is it the anticoagulant reported by De Suto Nagy (*Am. J. Physiol.* 141, 338, 1944) since it is not counteracted by Reinecke salt.

Lymph from the unburned leg was usually not affected. Changes in blood clotting time were rare, and in the few cases when a change was observed, it was too small to warrant serious consideration.

OVERMAN, RICHARD R. (Memphis, Tenn.). Reversible permeability alterations in febrile disease.

Although alterations in the distribution of native ions (Na, K, Cl) in the body have been reported in numerous diseases, the underlying mechanism of such changes has been elusive. The studies to be reported elucidate one of these mechanisms hitherto unsuspected in febrile disease.

In both fatal simian and therapeutic human malaria, the fluid available for dilution of NaSCN increases progressively throughout the febrile course until it equals the calculated total body water (approximately 65% of the body weight).

This increase in 'available fluid' is due to entrance of SCN into tissue cells as is shown by (1) amounts of SCN found in liver, heart, spleen, and skeletal muscle were far larger than could have been resident in the 'chloride space', and (2) time-concentration curves of NaSCN in plasma were no steeper than normal, indicating no increase in destruction or loss of SCN from the body.

Flame photometric measurements of Na and K distribution and chemical determination of Cl likewise reveal alterations in cellular permeability in febrile disease—the magnitude of such changes being dependent upon the severity. The erythrocyte Na and Cl may increase 100% while cell K falls a similar amount as the disease progresses.

Febrile disease in general may be accompanied by severe permeability alterations since changes in the *apparent* extracellular fluid volume are found (1) following prolonged typhoid vaccine injection

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in dogs, (2) in human patients with spotted fever, and (3) in bacteremias accompanied by temperature elevations.

The reversible nature of these permeability changes is revealed following chemotherapy in malaria and spotted fever. In both, the NaSCN space returns slowly to normal and in malaria the ionic concentrations likewise return to normal ranges.

The adrenal cortex may be involved in permeability changes due to fever since it has been shown by others that similar native ionic shifts, occurring in the blood of patients subjected to pyrexia induced by hyperthermy, can be prevented or reduced and the patients better withstand high body temperatures if treated prophylactically with adrenal cortical preparations.

These indications of reversible cellular permeability alterations introduce a new interpretation of fever and its effect upon ionic shifts. The entrance of Na and Cl into cells and the loss of K from cells to the degree demonstrated may well be accompanied by severe metabolic disturbances leading toward a fatal outcome.

Death from hyperpyrexia may be due to alterations in cellular permeability with concomitant enzyme system disturbances since we have demonstrated severe changes in cell Na, K, Cl (and SCN) in pyrexial state.

OWREN, P. A. (Oslo). **New factors concerned in the coagulation of blood.**

An account is given of a case of hemorrhagic diathesis due to a greatly prolonged coagulation time. It is demonstrated that the coagulation disturbance does not result from quantitative or qualitative changes of prothrombin, thrombokinese, calcium, or fibrinogen, or from the presence of coagulation-inhibiting substances.

The derangement of the coagulation process was due to lack of a hitherto unknown fifth coagulation factor, termed factor V, which is found in normal plasma, is thermolabile, and is important in the formation of thrombin. The properties and mode of action of this factor are demonstrated.

The velocity of thrombin formation increases with increasing concentrations of factor V until a certain limit. Without factor V no thrombin is formed.

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It is further shown that during the formation of thrombin a new factor is formed, termed factor VI, which together with calcium transfers prothrombin to thrombin. The effect of factor V and thrombokinase may be explained by the significance of these factors in the formation of factor VI. The formation of factor VI takes place as an autocatalytic reaction.

ROMIJN, C. (Utrecht). Foetal respiration in birds.

From the work of *Romijn* and *Roos* we know that the air space in the hen's egg increases in volume during the time of incubation and at the end of this time a volume of about 10 c.c. of gas may be collected. In the fresh laid egg the quantity does not exceed some tenths of a c.c. A method has been developed to determine the composition of the gas in the air space in one and the same egg throughout the incubation time. Moreover, the total gas pressure could be measured and was found to be nearly one atmosphere. During the last day of incubation the O_2 percentage in the air space is extremely low (about 9% or less) and the carbon dioxide percentage very high (up to 9.11%).

In recent years the author studied more intensively the physiological conditions during this last day of foetal life. The respiratory movements of the chick could be recorded optically from the fluctuations in gas pressure in the air space during the 'parafoetal period', when the true foetal respiration by means of the allantoic vessels is gradually superseded by the lung ventilation. A steady increase in respiratory rhythm could be detected, sometimes interrupted by heavy movements of the whole animal. The moment of perforating the shell could be recorded. When the air of the incubator enters the air space there will be a sudden rise in oxygen content and a fall in carbon dioxide content of the inspired air, though no influence on the respiratory rhythm could be detected. The chick, replaced in an atmosphere equal to that of the parafoetal period, shows a normal further delivery.

The permeability of the shell for different gases has been measured by means of an accurate differential method. During the time of incubation the part of the shell which covers the air chamber

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becomes more permeable than the other part. With a special technique, data about the gas diffusion through this part of the shell of one and the same egg during the incubation time could be collected. In the unfertile egg no increase in permeability could be established. The cause of this difference, which is of great physiological importance will be a subject of further researches.

From the figures, obtained with the diffusion experiments, the oxygen consumption of the chick could be calculated and the result is in good accordance with data, collected by *Needham* from the work of *Hasselbalch* and others, on the respiratory metabolism of the incubated egg.

DE SOTO-MORALES, F. F. (Madrid). Physiological conception of hypervitaminosis.

We intended to reproduce experimentally on omnivorous animals the so-called hypervitaminosis D₂, using the crystallized vitamin, but success was not achieved, in spite of the overdoses employed. We could only produce unspecific syndromes of toxæmia, with overcharge of steroids and secondary actions on diverse organs, which are not peculiar to the vitamin D₂, as they can be produced by other substances and do not affect the mechanisms which are usually influenced by this vitamin.

These pathological alterations, not specific to the vitamin, cannot really be called hypervitaminosis. Hypervitaminosis may be said to exist when the overdose of a vitamin produces an overfunction of the physiological mechanisms it usually protects. Neither can syndromes of overfunction be produced with an overdose of water-soluble vitamins. The hormones, however, do act when an overdose is given, producing specific syndromes of overfunction.

These facts show a basic difference in the form of reaction of the organism when receiving substances of exogenous source (vitamins, proteins, lipides, glucides) and of an endogenous one (hormones).

The organism has a mechanism regulating consumption of the substances it receives and usually consumes, and a mechanism regulating production of the substances it produces itself.

When we administer overdoses of substances of endogenous pro-

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duction (hormones) obtained from other animals, these are used directly without any regulation of consumption, because the organism, which supposes itself to be sufficiently protected by the 'production regulating mechanism' of its own glands, does not foresee the entrance of hormones from outside, and all that are introduced or are produced pathologically act without restriction, producing syndromes which are specific to hyperfunction and which cannot be reproduced by other substances.

When, however, we administer overdoses of substances of exogenous source and of a constant physiological consumption (provitamins, vitamins, proteins, lipides, glucides) only that amount which is physiologically necessary is used through the mechanism regulating consumption. A temporary overcharge is produced, and the reduction to the normal amount is arrived at by the excess being eliminated as a foreign substance without any specific energetic or enzymatic action. In some cases, however, non-specific disturbances can be produced: for example, if a diet of 50,000 calories is swallowed; nevertheless, indigestion and elimination troubles may follow, and these may be produced by the most diverse substances.

STELLA, G. (Padova). On the mechanism of Luciani's cerebellar 'atonia'.

In previous communications (Stella^{1,2}) it was shown, in cats and dogs, that the decerebrate rigidity of the fore-limbs disappeared after section of the posterior spinal roots C. V to Th. II, but it developed again if the inhibitory influence of the cerebellum upon the tonic labyrinthine reflexes was removed, either by ablation of the organ or by a complete transection of the cord at the last thoracic segment. Also deafferentation of the hind-limbs had the same effect as the removal of the cerebellum.

The decerebrate rigidity described by Pollock and Davis³ in deafferented limbs was due to the fact that their 'anemic' method of decerebration puts out of action the anterior lobe of the cerebellum. Cardin⁴ in this laboratory has further found that so far as decerebrate rigidity is concerned the deafferented hind-limbs behave in the same way as the fore limbs: they became rigid after decerebellation or deafferentation of the fore-limbs.

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The degree of rigidity in deafferented limbs after removal of the cerebellum has here been used as a test for the efficiency of the tonic labyrinthine reflexes in the chronic decerebellate animal presenting Luciani's atonia.

In 8 dogs the whole cerebellum was ablated. After 1 to 6 months the animals, which all presented a typical cerebellar syndrome, were decerebrated in front of the posterior colliculi. The usual rigidity developed in all limbs. The fore-limbs were now deafferented with the result that they lost their rigidity and remained flaccid even after transection of the cord at the last thoracic segment.

In other 4 dogs only one lateral half of the cerebellum was ablated. Decerebration carried out 5 weeks later was followed by a good rigidity in the 4 limbs. Both fore-limbs after deafferentation became flaccid. Section of the cord at the last thoracic segment caused the rigidity to reappear only in the fore-limb of the same side as the lateral half of the cerebellum still intact. Also when this last part was removed the contralateral fore-limb remained completely flaccid.

It appears, therefore, that in the chronic decerebellate animal the tonic labyrinthine reflexes are greatly diminished, a fact which must be taken into account when trying to explain cerebellar atonia.

In the above animals, section of the spinal cord did not abolish the rigidity in the hind-limbs, showing that the local spinal mechanisms for the stretch reflexes were hyperexcitable, probably as a compensation for the weakness of the labyrinthine reflexes.

¹ Stella, G., *Atti Soc. Med. Chir. Padova.*, 23, 5 (1944). ² Stella, G., *Boll. Soc. It. Biol. Sper.*, 22, 78 (1946). ³ Pollock and Davis, *Am. J. Physiol.*, 96, 47 (1931). ⁴ Cardin, A., *Boll. Soc. It. Biol. Sper.*, 22, 81 (1946).

VÁVRA, RUDOLF (Hradec Králové, Czechoslovakia). The measurement of the intensity of light reflected by the skin.

Although measurements of the intensity of light transmitted by the lobes of the ear were known to have been in use,^{1,2} I attempted to work out a method by which the intensity of light reflected by any portion of the skin could be measured.^{3,4,5} For this purpose, three filters for the red, yellow and blue parts of the spectrum and a Lange's reflectometer with a selenium photo-cell are being used.^{6,7}

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If the constancy of the light is reasonably secure, the sensitivity of the method amounts to 4×10^{-8} amperes.

The logarithmic ratio of the intensities of the light emitted and reflected are E_r /red filter/, E_y /yellow filter/, E_b /blue filter/. The smoothness, the wetness and the elasticity of the skin, the reflecting layers, the dispersion of the light, the pigmentation and the blood supply of the skin are variables. From this it is clear that for the purpose of determination of the concentration of a certain coloured matter in the skin, at least two filters will be needed, since one filter only would not compensate the changing nature of so many variables.

The concentration of the haemoglobin is given by
$$\frac{A \cdot (E_r : E_y - 1)}{E_y}$$
.

(The relation to the concentration of haemoglobin is illustrated by the figure.) The error in the determination of haemoglobin in human skin does not exceed $\pm 5\%$. At room temperature of 20°C . $0.2-0.98\%$ of haemoglobin was found under the human skin epithelium in a depth of 0.1 mm .

The ratio $E_y : E_b$ is dependent on the percentage of the reduced haemoglobin. The ratio is invalid, when there is present in the skin another coloured matter which increases the absorption of the blue light /bilirubin/. In case of acrocyanoses at least $0.25 \text{ g.}\%$ of reduced haemoglobin were being estimated.

Further, the actual pigmentation of the skin can be studied from the expression
$$\frac{1}{E_r(E_r : E_y - 1)}$$
. If the white filter paper has one unit of actual pigmentation, the number of units of the investigated place on the skin indicates to what extent this place appears to be darker than the filter paper. The actual pigmentation of the skin of white men thus determined in winter amounted from 3 to 15 units. The magnitude of the expression $(E_r : E_y - 1)$ determines amongst other things the amount of the red light reflected from the surface of the skin, without having penetrated to the pigmentation layers.

¹ Kramer, K., 'Ein Verfahren zur fortlaufenden Messung des Sauerstoffgehaltes im strömenden Blute in uneröffneten Gefäßen', *Ztschr. f. Biol.* 96, 126 (1934); 96, 61 (1935).

² Matthes, K., 'Untersuchungen über die Sauerstoffsättigung des menschlichen Arterienblutes', *Arch. f. exper. Path. u. Pharmacol.* 179, 698 (1935).

³ Vávra, R., 'Reflektometrie kůže', *Čes. derma-*

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tologie, 5, 111 (1947). ⁴ Vávra, R., 'Hodnocení reflektometrických výsledků', *Biologické listy*, in print. ⁵ Vávra, R., 'Použití reflektometrie v lékařství', *Biol. listy*, in print. ⁶ Lange, B., *Photoelements and Their Application*, New York, 1938, Reinhold Publication Corporation. ⁷ Nygaard, K. K., *Hemorrhagic Diseases*, St. Louis, 1941, The C. V. Mosby Company.

DE WAELE, HENRI P. L. (Ghent). *Insuline et contrainsuline.*

On peut extraire du pancréas une substance fixée sur une graisse et qui peut en être détachée en gardant son activité; elle est alors soluble dans l'alcool. Sous les deux formes on peut l'administrer en injection ou 'per os'.

Chez le chien, chez le lapin, le chat, le rat, la grenouille, elle détermine une augmentation du métabolisme et des expériences qui sont réalisables chez le rat montrent que l'augmentation porte surtout sur les glucides et les lipides.

Elle provoque un léger degré de glycosurie. Mais l'urine n'évacue que 10 à 20% de ce qui disparaît du foie: le reste doit donc se fixer et de fait on trouve une augmentation de la teneur en graisse dans le foie et dans les muscles (ce dernier point est surtout net chez la grenouille).

A forte dose elle produit chez le chien un état subictérique et une tendance à diarrhée.

A part la glycémie elle n'agit ni sur le sang, ni sur la coagulation ni sur la pression sanguine. La thyroïde ni les surrénales n'interviennent pas, même indirectement. Elle est inactive in vitro.

Chez la grenouille l'injection diminue la teneur du foie en glycogène, laquelle tombe parfois à 0 en 48 heures.

Si à l'injection chez la grenouille on ajoute 20 ctg. de glucose, l'animal ne fixe pas ce glucose, mais le foie s'appauvrit encore en glycogène. Sur ce fait on peut baser une méthode de *test* dans la préparation et la purification du produit.

Nous proposons de désigner cette substance comme *contrainsuline pancréatique* pour la différencier de la contrainsuline de *Houssay* et *Biasotti* provenant de l'hypophyse. Elle paraît donc réaliser avec l'insuline l'équilibre compensateur de fixation et de libération des hydrates de carbone dans le foie et dans l'organisme et il y aurait peut-être lieu d'en tenir compte dans les théories du diabète.

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WEISS, PAUL (Chicago). **Protoplasm synthesis and substance transfer in neurons.**

Evidence collected from over 100,000 mammalian nerve fibers, subjected to various degrees of chronic constriction with or without attending regeneration, has led to the following conclusions:

1. Medullated axons are entertained in a continuous state of growth and replacement whereby new axoplasm is produced in the nucleated central cell body and conveyed distad, where it is used up, presumably in the functional decay of enzyme and other protein systems.

2. The rate of central synthesis is governed by the terminal connections of the axon.

3. The rate at which the axonal material can move distad varies with the cross section of its channel, the neurilemmal tube. Therefore:

4. Reduction of the fiber lumen causes the more distal parts of the axon to remain permanently undersized (e.g. decline from $10\ \mu$ to $2\ \mu$).

5. In contrast, the axon portion proximal to the constriction becomes greatly oversized (e.g. increase from $10\ \mu$ to $40\ \mu$) by the piling up of excess axoplasm with resulting contortions of the myelin sheath.

6. Varied experiments, including radioisotope tracer experiments, and a mechanical analysis of the damming process prove its causation by pressure dynamics inside the nerve.

7. Upon release of the constriction, the piled up axonal material moves distad into the narrow portion, the front of this tidal wave advancing at a rate of the order of 1 mm. per day or less.

These experiments reveal the body of the neuron as of much less static and much more adaptable constitution than has generally been realized—a fact which may influence our concepts of central and mental functions.

WILSON, WM. H., and SAMAAH, ADLI (Cairo). **The origin of the polypnoea resulting from multiple pulmonary emboli.**

There is an unexplained fact in the physiology of respiration, namely, that section of the pulmonary vagi and moderate deflation of the lungs, which are alleged to bring about complete disappearance of the action potentials from the lung tissue, have diametrically opposite results.

According to our view, the polypnoea accompanying deflation is due to the excitation of vagal nerve endings in the lungs other than those excited by inflation causing inhibition; and that the slowing following vagotomy is due to the cutting off of a tonic excitatory influence which is of functional importance in normal breathing. The impulses arising in these two types of nerve endings are carried by different nerve fibres and have opposite effects on the respiratory centre, the one inhibitory controlling the depth and the other excitatory maintaining the rate of breathing.

The polypnoea caused by multiple pulmonary emboli bears a strong similarity to that produced by deflation of the lungs, since both are (a) definitely of *pulmonary* origin, (b) are not caused by changes in the auricular pressure, (c) are not caused by changes in the arterial or pulmonary blood pressure, (d) are not due to alterations in the composition of the blood, (e) are independent of impulses from the vasosensory areas, and (f) are not evoked from the cardiac receptors. The only factor which abolishes the effects of both the deflation and the multiple pulmonary emboli is the section of the pulmonary branches of the vagi.

It is legitimate to assume that both might be caused by the same fundamental mechanisms. This suggestion is supported by the observation that partial freezing (i.e. cooling the nerve to 6° C.) of the vagi cuts out the inflation inhibitory fibres but has no effect on either of the other two reactions. Moreover, ethyl aceto-acetate was found to evoke both excitatory and inhibitory respiratory responses from the lung tissue. The inhibitory action alone could be readily abolished by cooling the vagi to about 6° C.

From these studies we came to the conclusion that, unless quite new explanations are advanced for the first phenomenon, we do not see any other possibility to explain the effect of multiple pulmonary

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embolism except by suggesting that it causes stimulation of the excitatory accelerator fibres in the pulmonary tissue.

The evidence of the correctness of this conclusion will be discussed in the communication.

YOUNG, J. Z., VIZOSO, A. D., and SHEPHARD, R. H. (London).
The structure, spacing and significance of the nodes of Ranvier.

The nodes of Ranvier are interruptions of the coating of myelin without any break or membrane across the axon. The protoplasm of one Schwann cell covers each internode and the neurilemmal tube wall turns in at the node to make a ring, the so-called cementing disc, which does not extend into the axoplasm. Nodes occur on fibres of all sizes in vertebrate peripheral nerves but not on fibres of the central nervous system. They are present in the medullated nerves of prawns but only on the larger fibres. They are also absent from regenerating nerve fibres in the early stages of myelination.

In a normal mammalian nerve the internode length increases with fibre diameter but at a rate which varies in different nerves. In Man the smallest fibres ($2-3\ \mu$) have internode length about $300\ \mu$; the larger fibres, say $15\ \mu$, have internode length up to $1.3\ \text{mm}$. in the anterior tibial and ulnar nerves, $0.7\ \text{mm}$. in the mandibular nerve. The slope of the line relating internode length to diameter is therefore steeper in the faster-growing nerves. This suggests that when myelin is first laid down on the fibres of $1-2\ \mu$ diameter the internode length is about $200\ \mu$ and the extent to which it increases depends on the amount by which the nerve is subsequently stretched during growth.

Observation of developing and regenerating nerves confirms this view. The increase of internode lengths during development is proportional to the growth of the part. Regenerating nerve fibres are at first covered with a continuous sheet of myelin which then breaks into segments about $200\ \mu$ long, varying considerably. Although the fibres subsequently increase in diameter the internode length remains short. Sanders and Whitteridge have shown that these large fibres with short internodes conduct as rapidly as normal fibres of the

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same diameter. Nodes and internodes are therefore probably not of critical importance for conduction, as is suggested also by their absence from many medullated fibres.

These observations suggest that the nodal arrangement arises from the behaviour of the myelin as a liquid, occupying the space between the turgid axon and the rather rigid tube wall which surrounds a peripheral nerve fibre. On developing or regenerating fibres, the ends of the myelin at the nodes leave a large area of axon bare. As the diameter increases and more myelin is produced, the material is squeezed into the characteristic adult shape. There may be a temporary breaking up of the myelin into drops during development. Internodes of twice and half normal length occur occasionally, and would be expected to form by the breaking or fusion of the long drops. The shape of the myelin drops therefore depends on their physical properties and wetting powers under the influence of the outward pressure of the axon, inward pressure of the tube wall and longitudinal tensions during growth. This analysis confirms and extends Ranvier's view that the myelin is a drop included in the Schwann cell as the fat is in a fat cell. The basic stable length of drop appears to be about $200\ \mu$ for fibres of $2-3\ \mu$ diameter. The functional significance of the segmentation remains obscure but the division may serve to reduce the danger that the myelin should become pushed longitudinally, as is liable to occur in peripheral nerves.

ANREP, G. V. (Cairo). A potent coronary vasodilator of Egyptian origin.

Several crystalline substances have been extracted by various authors from the seeds of *Ammi Visnaga*, an umbelliferous plant growing widely in the Middle East. Extracts of this plant have been in use by the population since ancient times as an antispasmodic in cases of ureteral calculi. *K. Samaan* has demonstrated that some of these crystalline principles cause a relaxation of visceral plain muscles. *Spaeth* and *Gruber* showed that the chemical structure of these substances bear a strong relation to each other. They all belong to the group of furo-chromones containing different numbers of methoxy groups.

In collaboration with Drs. *Bagoury*, *Barsoum*, *Kenawy*, *Misrahy*,

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and *Fahmy*, we have investigated the comparative action of crystalline derivatives of *Ammi Visnaga* on the coronary blood flow. It was found that khellin, a di-methoxy-methyl-furo-chromone, is a powerful coronary vasodilator, the minimal active concentration of which is 10^{-4} . The drug has a very prolonged action and is excreted or destroyed in the body extremely slowly. Methods of quantitative estimations of khellin in blood were devised and it was shown that, on administration to human subjects, its concentration in the blood can reach $15 \mu\text{g./cc.}$ Khellin also causes a conspicuous relaxation of bronchi. A comparative study of the action of khellin, of other related compounds and of their derivatives has been made.

Khellin has been satisfactorily used in human subjects to alleviate the symptoms of angina pectoris and of bronchial asthma.

BARER, ROBERT (Oxford). The contractility of myofibrils.

If single striated muscle fibres are observed microscopically during normal contraction, the cross striations may shift their position or change in thickness but as a rule they remain straight and extend right across the width of the fibre. This is presumably due to a synchronous contraction of all the myofibrils, so that the cross striations of each individual myofibril remain in alignment with those of neighbouring myofibrils. It is possible, however, to cause the myofibrils to contract asynchronously so that the normal cross striated appearance is lost. This can be done (1) by certain types of electrical stimulation using non-polarizable micro-electrodes, which may cause a localized contraction of only a fraction of the myofibrils or (2) by immersion of the fibres in certain solutions, for example, slightly alkaline Ringer solution. In favourable circumstances a rhythmic asynchronous contraction of groups of myofibrils can be observed.

These observations offer evidence in support of the existence of myofibrils as separate entities in living fibres and show that they are individually contractile. The presence in normal fibres of some mechanism to ensure synchronous contraction of myofibrils is presumed.

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BARKER, JØRGENSEN, C. (Copenhagen). The effect of adrenaline on the permeability of frog skin to ions.

Isolated skin of the frog (*Rana temporaria*) was bathed on its physiological inner side with frog Ringer and on its physiological outer side with water or dilute salt solutions. Such preparations lose salt at a moderate rate. The loss is markedly increased on addition of adrenaline to the Ringer solution. The effect can even be demonstrable with adrenaline diluted to about $1:10^6$. Adrenoxyl. $1:10^6$ and ephedrine $1:10^6$ are without any effect. In contrast to adrenaline, ephedrine $1:10^6$ increases the permeability of the skin irreversibly.

BARTORELLI, CESARE (Parma). Recherches électrocardiographiques sur l'allure de la fréquence cardiaque pendant et après la stimulation du cervelet chez le chat thalamique.

Moruzzi¹ vient d'observer que la stimulation faradique légère de certaines régions bien déterminées du cervelet est suivie chez le chat thalamique par des manifestations neurovégétatives parfois importantes. Si la préparation est très excitable on observe un accès de *sham rage* après la fin de la stimulation, c'est à dire dans la période du *rebound* cérébelleux; pendant la stimulation la *sham rage* est au contraire inhibée. Toutefois si l'animal était tranquille on n'observe aucune manifestation importante pendant la stimulation; et le *rebound* neurovégétatif est alors la seule preuve que les centres hypothalamiques ont été ébranlés par les influx cérébelleux. Si la préparation est peu excitable on observe seulement des réponses neurovégétatives locales, qui intéressent notamment la pupille et la membrane nictitante.

Nous avons voulu étudier dans ces conditions expérimentales l'allure de la fréquence cardiaque et nous avons essayé de mettre en rapport nos observations avec les manifestations neurovégétatives décrites par Moruzzi. La fréquence du cœur était calculée pour chaque pulsation en mesurant l'intervalle RR. La stimulation faradique du cervelet était faite avec la technique de Hess. La localisation et l'intensité de la stimulation ont été les mêmes que dans les recherches de Moruzzi.

Nous n'avons pas observé des modifications de la fréquence

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cardiaque pendant et après la stimulation cérébelleuse dans les cas de réponse neurovégétative locale. Le *rebound* cérébelleux peut être caractérisé par une dilatation pupillaire très marquée avec nette rétraction de la membrane nictitante sans qu'on puisse observer la moindre accélération de la fréquence du cœur. Nous rappelons à cet égard que *Gellhorn*, *Cortell*, et *Murphy*² ont fait les mêmes observations en stimulant les centres hypothalamiques; il paraît que les centres végétatifs oculaires soient plus aisément ébranlés que les centres cardiaques.

Lorsque la stimulation cérébelleuse inhibe ou déclenche la *sham rage* on observe des modifications de la fréquence du cœur. La violence des mouvements de l'animal nous a souvent empêché d'en enregistrer l'électrocardiogramme. Dans quelques cas nous avons réussi toutefois à obtenir des résultats très nets. La fréquence du cœur passait de 150-60 à 200-20 pendant l'accès de *sham rage* produit par le *rebound* cérébelleux. Pendant la stimulation la fréquence ne changeait pas appréciablement si l'animal était tranquille, mais on observait une diminution de la fréquence cardiaque lorsque le stimulus était appliqué pendant un accès de *sham rage*.

Il nous paraît très probable que les modifications de la fréquence cardiaque, comme les manifestations de *sham rage* observées par *Moruzzi*, soient dues à une action directe du cervelet sur les centres hypothalamiques.

¹ *Proc. of the XVII Int. Physiol. Congress, Oxford, 1947.*
Physiol. 146, 376 (1946).

² *Am. J.*

BUSSARD, ALAIN, et GRABAR, PIERRE (Paris). Étude immunologique des gonadotrophines de gestation.

L'activité antihormonale est actuellement assimilée à un phénomène d'immunité. Cependant la preuve d'une précipitation spécifique de l'hormone elle-même restait à faire. Nous avons pu obtenir régulièrement des sérums de lapins anti-gonadotrophines chorales qui, outre la propriété d'inactiver l'hormone, possédaient le pouvoir de précipiter l'antigène immunisant. Ceci a été réalisé grâce à une administration intraveineuse de l'hormone associée à de l'alumine colloïdale.

Nous avons étudié en détail l'activité physiologique du précipité

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hormone-sérum antihormone résultant d'un contact de un à trois jours et soigneusement lavé. Lorsque ce précipité est obtenu en présence d'un excès d'anticorps, il semble, injecté à des rats impubères, ne pas avoir d'activité gonadotrope. Par contre, lorsqu'il s'agit d'un précipité obtenu en présence d'excès d'antigène, celui-ci est doué d'une activité gonadotrope notable. Dans ces conditions, le liquide surnageant est également physiologiquement actif, mais les eaux de lavage du précipité, bien qu'entraînant des produits azotés solubles, n'ont aucune activité. D'autre part, lorsqu'on laisse en contact le sérum anti et l'hormone pendant plus d'une semaine, le précipité obtenu ne possède plus d'activité.

Quoiqu'il en soit, l'activité hormonale du précipité convenablement lavé et le fait que les eaux de lavage n'entraînent aucune activité, semblent ne pouvoir s'expliquer que par la présence de l'hormone dans un complexe spécifique au sein de ce précipité.

On voit que l'étude quantitative de la réaction hormone-antihormone (données complétées par des dosages d'N du précipité) ne permet pas de relever, entre ce phénomène et le phénomène classique de la neutralisation des antigènes (réaction toxine-antitoxine par ex.), de différence notable, et qu'en conséquence il n'y a pas de raisons objectives d'établir une distinction essentielle entre antihormone et anticorps.

TEN CATE, J. (Amsterdam). L'Influence des organes périphériques sur l'activité électrique de la moëlle épinière.

L'activité électrique spontanée de la moëlle épinière chez la grenouille a été décrite pour la première fois par Gerard et Young (1937). En collaboration avec les docteurs G. P. M. Horsten, W. G. Walter, et l'ingénieur L. J. Koopman, j'ai exécuté des expériences pour examiner de près ce phénomène intéressant. Nous avons pu démontrer que l'activité électrique, soi-disant, spontanée de la moëlle est soutenue principalement par des excitants qui l'atteignent par les nerfs centripètes sensitifs. Lorsque tous les nerfs sont sectionnés, donc après une isolation complète de la moëlle, l'activité électrique spontanée est toujours considérablement réduite.

Il nous semblait important de savoir si ces stimuli périphériques

venaient de la peau ou des muscles striés. Ensuite nous voulions examiner si l'extension de la peau ou bien des muscles des extrémités postérieures pouvait avoir un effet sur l'activité de la moëlle.

Pour l'enregistrement des variations de potentiel de la moëlle nous avons utilisé un électrocardiographe à amplificateur de Siemens muni d'un préamplificateur. La dérivation était du type monopolaire. L'électrode 'active' fut placée sur la colonne vertébrale au-dessus de la moëlle, tandis que l'électrode 'indifférente' fut appliquée sur l'extrémité pelvienne du dos. L'activité électrique fut enregistrée de la partie postérieure de la moëlle, après que la partie antérieure et le cerveau avaient été extirpés.

Premièrement nous avons enregistré l'activité électrique de la moëlle chez des grenouilles couchées sur une petite table dans une position horizontale. Après cela sans déplacer les électrodes, par un mouvement d'une partie de la table vers le bas les pattes postérieures furent mises dans une position verticale; de sorte qu'elles pendaient librement en bas. L'activité électrique de la moëlle n'augmenta pas beaucoup. L'extension des muscles et de la peau n'a pas une grande influence sur l'activité électrique de la moëlle.

Dans des expériences subséquentes nous pouvions établir que lorsque la partie postérieure de la grenouille est dépouillée de sa peau l'activité électrique de la moëlle diminue notablement. Nous avons obtenu les mêmes résultats après l'application du curare.

Comme il ressort de nos expériences l'activité électrique de la moëlle épinière chez les grenouilles est soutenue principalement par des stimuli proprioceptives ainsi que extéroceptives. Après l'élimination des excitants afférents il reste l'activité électrique proprement spontanée, laquelle est toujours beaucoup plus faible que chez l'animal normal.

COOKE, W. T., BARCLAY, J. A., and KENNEY, R. A. (Birmingham). The tubular excretion of urea in man.

Simultaneous clearances of inulin, creatinine, and urea have been determined on a number of patients suffering with varied pathological conditions of the kidney. A group of these patients, with chronic renal disease and not in a terminal state of uraemia, showed

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clearances of urea greater than those of both inulin and creatinine. Further confirmation of the results were obtained from the diodone clearances (at T_m levels) which were also lower than the urea clearances.

It would appear unlikely that three different chemical substances, inulin, creatinine, and diodone, would diffuse back in the damaged tubules at rates sufficient to give similar clearances. Hence the theory that such substances diffuse back into the circulation faster than urea is unacceptable. An alternative explanation is put forward that urea is secreted by the tubules. Such a process is adopted by the human kidney as a compensatory mechanism for a state of glomerular insufficiency, relative to tubular function, in certain chronic renal disorders.

EBERHART, H. D., INMAN, V. T., RALSTON, H. J., and SHAFF-RATH, M. D. (San Francisco). **Length-tension relationships in isolated human voluntary muscle.**

The length-tension relationships, under isometric and isotonic conditions, have been determined for certain voluntary muscles of human subjects who have suffered amputation of the arm. In the isometric studies the free ends of such muscles, extended various distances, were fastened to rigid metal rings, the distortions of which were measured by strain gages, and recorded oscillographically. The muscle contractions were purely voluntary in nature. Simultaneous electromyograms were recorded to insure a constant degree of muscular effort, and precautions were taken to prevent general bodily movements confusing the results. In the isotonic studies, known loads were moved through measured distances, with similar precautions being observed.

Using the same techniques, supplemented with X-ray data for determining the lengths of muscles and lever-arms, the length-tension relationships, under isometric conditions, in voluntary muscles of the normal human subject have been determined.

In general, the experimental curves agree with those of earlier studies of frog whole muscle and isolated muscle fibers, artificially stimulated.

Certain implications of these results for normal voluntary movement are discussed.

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HALL, F. G. (Durham, N.C.). **Respiratory efficiency at altitude.**

Exchange of gases in the lungs of man has been studied in simulated altitudes up to 44,000 ft. while breathing oxygen at ambient pressures. Pulmonary ventilation is not increased significantly at altitudes below 38,000 ft. but above that height anoxia leads to deeper breathing. A compensation or accommodation to high altitudes leads to a higher saturation of the blood with oxygen. Individuals acclimatized to 5,000 ft. altitude are adjusted to a different level of gas exchange than those individuals living at sea level. Acclimatization in these cases results from changes in the alveolar air rather than in the virtual equilibrium which appears to exist at all altitudes between alveolar air and blood. Moderate exercise seems to have little effect upon arterial saturation at altitudes up to 40,000 ft. in subjects breathing pure oxygen.

KONZETT, H., and VERNEY, E. B. (Cambridge). **Observations on the urine and blood of dogs before and after the production of renal ischaemia.**

Lockett (1946)¹ describes the appearance of a new base, detected by a colour test and indicated as *x*-positive base (*x*), in the urine of bitches after partial obstruction of the renal artery, this base not being present in normal dog or human urine. *x* was measured in terms of ephedrine HCl by *Richter's* (1938)² toluene extraction method and expressed as ephedrine HCl equivalent (EE). *Lockett* reports that the blood became *x*-positive during renal ischaemia and, in long-term experiments, that the fall of B.P. to normal synchronized with the disappearance of this compound from the blood, but its presence in the urine continued. Further, when the B.P. was raised by limitation of fluid intake and by administration of simple salts, there was an accompanying rise in *x* in the blood and fall in the urine, effects which were found to be reversible.

Lockett's results seemed to us of such importance as to merit a repetition of those experiments on which her primary findings are based. We have been unable to confirm them.

We first investigated repeatedly the urine of five bitches: it was *x*-positive in every instance, the amount of *x* per c.c. urine varying between the wide limits of 0.8 and 30×10^{-4} g.EE and the hourly output lying between 0.1 and 2.8×10^{-4} g.EE. Moreover, the blood of three of these was examined; in each instance it was faintly *x*-positive. Long-term observations were then made on two animals. In the one (e.g.) the hourly *x*-output varied between 0.1 and 1.5×10^{-4} g.EE: its B.P. was 120 mm. Hg. After partial obstruction of the right renal artery the B.P. was between 150 and 160 mm. Hg., the hourly *x*-output showed no significant change, nor did *x* increase in the blood. The blood-supply to the left kidney was then partially obstructed. The B.P. rose to between 176 and 184 mm. Hg., the hourly *x*-output varied between 0.1 and 1.6×10^{-4} g.EE, and the *x*-content of the blood was certainly no higher than before the first operation.

In short-term experiments, too, no significant change occurred

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either in the x-output in the urine or in the x-content of the blood during partial obstruction of one renal artery.

¹ Lockett, M. F., *J. Physiol.* 105, 126 (1946). ² Richter, D., *Biochem. J.* 32, 1763 (1938).

KORENCHEVSKY, V. (Oxford). **Effects of simultaneous administration of sex and thyroid hormones on ageing in rats.**

The experiments were performed, jointly with Miss V. E. Jones, on female rats. It was found that in these animals (as in human beings) a relative hypoplasia of organs progressively develops with ageing.

Therefore this hypoplasia may be considered to be one of the essential features and indicators of the rate of ageing, and therefore was used as such in the present experiments. The changes in weights were confirmed and explained by histological examination of the organs.

It was found that ovariectomy hastens the process of ageing in the organs of rats. On the other hand, the administration of progesterone, oestrogenic, androgenic, and thyroid hormones in suitable doses and combinations produces an opposite, hypertrophying effect on some organs investigated, namely on liver, kidneys, uterus, vagina, and adrenals. This was demonstrated in the changes obtained in weight and histology of organs.

Taking into consideration the changes in all organs, the stimulating, and in a certain sense (in the case of 'ageing' hypoplasia), anti-ageing action on the organs examined produced more normal hypertrophic changes after simultaneous administration of androgenic, oestrogenic, and thyroid hormones. Pathological metaplastic changes, however, occurred in the uterus due to the effect of the oestrogenic hormones, which could not be prevented by simultaneous administration of androgenic and thyroid hormones, progesterone being necessary to counteract this effect. This indicates that the simultaneous activity of the hormones naturally present in the organism is essential for normal structure and, presumably, function of organs. This is not surprising if one remembers that in the organism all hormones are secreted simultaneously, producing a certain normal balance between these compounds. It is known that the upsetting of this balance is dangerous and this was also shown in the present experi-

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ments: for example, single administration of oestrogenic or thyroid hormones may produce depression of growth, or (oestrogens) metaplasia of uterine epithelium; single administration of androgenic hormones might produce atrophic changes in adrenals. These observations in rats suggest the desirability of their confirmation on human beings. If confirmed, pluri-hormonal treatment for general stimulation of the organism has to be investigated and might give better results than the present-day treatment, in which usually only a single hormone is administered.

It must be emphasized, however, that there is not much hope of successful treatment of old age with hormones for two reasons: (1) various causes, producing decreased function and morphological changes in tissues of the ageing organism, are acting from elsewhere and are not removed by stimulating these tissues or organs; (2) a degenerated or hypoplastic old organ or tissue cannot stand vigorous stimulation, but may collapse from paralysis (just as a tired horse, when whipped to do extra work, cannot withstand the strain and suddenly collapses from heart failure).

MORUZZI, GIUSEPPE (Parma). *Sham rage and localized autonomic responses elicited by cerebellar stimulation in the acute thalamic cat.*

The experiments have been performed on acute thalamic cats. Hess's technique has been used for stimulating the cerebellar lobes and the underlying white matter and for localizing the stimulated areas.

1. *Sham rage.* An outburst of sham rage (mydriasis, retraction of nictitating membranes, exophthalmos, widening of lids, vocalizations, increase of the arterial pressure, struggling movements, lashing of the tail) is observed, as a rebound effect, after the end of a weak cerebellar faradization (25-50 Kronecker units). During the stimulation there are no diencephalic responses, if the cerebellum is faradized in an interval of quiescence, but inhibitory effects are found when the stimulation is made during an outburst of sham rage. Sometimes the cerebellar inhibition is unable to overcome the sham rage, but the diencephalic discharges clearly increase after the end of the stimulation.

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2. *Localized autonomic responses.* When the preparation is deteriorated, strongly nociceptive stimulations are required to evoke rage reactions. The excitability of the cerebellum may then be very good, as shown by the tegmental responses, but mass discharges of the diencephalic centers are not to be expected as a consequence of a cerebellar stimulation. Localized autonomic responses of the eyes are, however, often observed in these weakened conditions and sometimes differential discharges may be obtained within the ocular autonomic centers (i.e. rebound dilatation of the pupil without retraction of the nictitating membrane).

3. *Localization.* The best results have been obtained from the white matter of the *Lobulus medius medianus*, but the *Pyramis* and the cerebellar lobuli just before the *Fissura prima* can give good responses. The cerebellum has not yet been fully explored, but the localization for the tegmental and for the diencephalic responses is certainly not the same.

4. *Spread of current.* It must be negligible because (i) the threshold was lower than for the motor cortex, (ii) silent areas have been found only 2 mm. before or behind strongly active spots, (iii) no rebound or biphasic response has been observed by faradizing the floor of the IV ventricle. Sympathetic ocular signs *during* the stimulation (Ferrier, Zimkina, and Orbeli) have been elicited only with strong stimuli and are easily duplicated by weak faradizations of the floor of the IV ventricle; they are probably due to the stimulation of bulbo-pontine fibers.

5. *Cerebellum and hypothalamus.* Hypothalamic centers are probably directly inhibited and activated by cerebellar impulses because (i) rage reactions are abolished by precollicular decerebration and (ii) somatic and autonomic responses have different thresholds and may be dissociated.

PIRENNE, M. H. (London). Visual acuity and the quantum nature of light.

The familiar fact that visual acuity—i.e. the ability of the eye to distinguish details—is generally higher at higher light intensities has not yet received complete explanation. The present investigation

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shows that the theory of the physical fluctuations occurring in the stimulation of the retina by light may have to become part of the explanation of this phenomenon. Experiments were made on human subjects at very low intensities under conditions of peripheral rod vision. The results agree quantitatively with the theory, according to which the observed change of visual acuity is due for the greater part to no other cause than the quantum nature of light itself.

The theory can be outlined as follows. When a retinal detector is exposed to light, there is only a certain probability p of its being excited, p going progressively from zero to unity as the intensity is increased. *Hecht, Shlaer, and Pirenne* have shown that under certain conditions the variation of p with intensity can be quantitatively accounted for by the purely physical fluctuations which occur in the small number of light quanta absorbed by the detector. Imagine then that a retinal area containing a number N of independent and identical detectors is illuminated for a short time. The probability of exciting one of the detectors being p , the mean number of detectors excited is pN and this number tends to N as p tends to unity. Thus, even though the detectors are quite identical, such a retinal mosaic would become *functionally* finer at higher illuminations. More detectors being then active per unit of retinal area, the resolving power of the retina must be higher.

The retinal detectors in the present experiments are *groups* of rods, each group acting as a physiological unit and being probably connected to one single optic nerve fibre. The experiments give for the size of these groups an independent estimate (diameter on the retina of the order of 0.6 mm., corresponding to a visual angle of about 2°) which agrees well with other determinations made by various methods in man and in some animals.

SCHEINFINKEL, N. (Bern). Die Erzeugung des langdauernden Tetanus am quergestreiften Kaltblütermuskel durch einen elektrischen Einzelreiz und die Beeinflussung desselben durch Eaerin, Kalium, und Insulin.

Zerstört man durch Köpfung des Frosches dessen Rückenmark unvollständig, so daß das reflektorische Zentrum für die Bewe-

gungen der hinteren Extremitäten noch eine zeitlang funktionstüchtig bleibt, entfernt dann die Haut der beiden Oberschenkel und läßt die freigelegte Muskulatur während der ganzen Zeit des Versuches in unmittelbarer Berührung mit der atmosphärischen Luft, so tritt schon nach etwa drei Stunden ein merkwürdiges Phänomen ein. Die Muskeln reagieren auf einen elektrischen Einzelreiz (Kondensatorentladung) nicht wie gewöhnlich mit einer Einzelzuckung, sondern sie kontrahieren sich tetanisch. Die Dauer des Tetanus beträgt zunächst 1–2 Sekunden, wird aber mit fortschreitender Versuchszeit immer länger und kann am Ende der sechsten Stunde nach Beginn des Versuches den maximalen Wert von etwa 40–60 Sekunden erreichen. Dieses Phänomen eröffnet interessante Ausblicke auf eine Reihe physiologischer Probleme und eignet sich zugleich sehr zur Prüfung, der so wichtigen Frage der humoralen Übertragung der nervösen Erregung, mit welcher sich auch die Untersuchungen der vorliegenden Arbeit befassen. Sie zeigen, daß der 'Eserineffekt' am Kaltblütermuskel auch unter den Bedingungen, wo der einzelne elektrische Reiz den langdauernden Tetanus hervorrufen kann, völlig ausbleibt. Auch die Vorbehandlung des Frosches und die direkte Bepinselung der zu untersuchenden Muskulatur entweder mit Acetylcholin oder Pferdeserum, welches bekanntlich reichlich Cholinesterase enthält, sind ohne Einfluß auf die Dauer und das zeitliche Auftreten der durch Einzelreiz veranlaßten tetanischen Kontraktion. Die mitgeteilten Ergebnisse schränken stark die Rolle des Acetylcholins als alleinigen chemischen Vermittler bei Reizung der motorischen markhaltigen peripheren Nerven ein, sie sollen aber keineswegs die chemische Theorie der Übertragung der nervösen Erregung als solche angreifen, sondern die von mir öfters vertretene Auffassung stützen, daß es sich bei der humoralen Übertragung der nervösen Erregung am Skelettmuskel nicht bloß um die Wirkung eines einzigen chemischen Vermittlers, nämlich des Acetylcholins, handle, sondern um eine 'Systemwirkung', wie wir sie auch auf andern biologischen Gebieten kennen.

Die Ausbildung des geschilderten Phänomens wird dagegen durch das Kalium und ganz besonders durch das Novoinsulin stark gefördert. Da nun das Insulin die Kaliumwirkung auf die Spannungsentwicklung des quergestreiften Muskels außerordentlich verstärkt,¹ erfahren die in den vorausgehenden Arbeiten² gezogenen Schluß-

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folgerungen von der eminenten Rolle des Kaliums für das Zustandekommen der Muskelkontraktion durch die erwähnten Versuchsergebnisse eine neue und kräftige Stütze.

¹ Scheinfinkel, N., *Helv. Physiol. Acta* 4, C (1946).

² Scheinfinkel, N., *Helv. Physiol. Acta* 2, C 50 (1944); 3, C 14, 27, 45 (1945).

SCHLAPP, W., and BRADLEY, K. (Manchester). **Serum potassium in cats under high CO₂ tensions.**

When carbon dioxide is administered to decapitated cats by artificial respiration at tensions increasing up to 300 mm.Hg. over a period of 4 to 6 hours the potassium content of the serum increases to about twice its normal value. When carbon dioxide is discontinued the serum potassium increases sharply and may reach three times the normal value in a few minutes, after which it falls again to the previous value of double the normal.

The first increase appears in eviscerated animals but the second does not, though it is seen if the hepatic artery and liver are spared. This suggests that the potassium may be of hepatic origin.

The second increase in serum potassium also appears to be dependent on the suprarenal glands, for it cannot be produced when they have been extirpated.

The increase of serum potassium on withdrawal of carbon dioxide is detectable when the animals have been subjected to tensions as low as 60 mm.Hg.

SINCLAIR, D., and FEINDEL, W. (Oxford). **Observations on the sensory changes induced by a pressure cuff on the arm.**

If a sphygmomanometer cuff is inflated at a pressure above systolic blood pressure on a human limb, a progressive loss of cutaneous sensibility occurs peripheral to the cuff. The work of *Lewis, Pickering*, and *Rothschild* in this connexion has been repeated and amplified. These authors describe a regularly ascending 'centripetal paralysis' and attribute this mode of spread to an increased susceptibility of the individual nerve fibres to the effects of pressure as they are traced proximally from the periphery. They further attribute the order of

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loss of the various sensory modalities in any area to a differing susceptibility of fibres of large and small diameter.

We have found that in the territory of any given nerve, loss of sensibility commences in different sites in different subjects and spreads irregularly, rather than centripetally. When the cuff encircles the arm, sensory loss occurs in the cutaneous areas of the hand considerably before it appears in the forearm. This may be attributed to a difference in the exposure to compression of the nerves supplying the skin of the hand and forearm respectively.

Experiments with cuffs in different situations on the upper limb fail to show that sensory loss begins any less quickly as the site of compression is moved distally on the arm. Sensory loss does, however, begin later when the cuff encircles the forearm, and this is also probably due to decreased effectiveness of compression at this site.

The order in which the various sensory modalities are lost in the ulnar cutaneous area has been investigated, and it is submitted that the hypothesis of varying fibre size susceptibility is inadequate to explain the results in detail. The manner in which any modality is lost appears to be fairly characteristic. Subjectively, there is first an alteration in the quality of the sensation, then prolongation of the response followed by delay in appreciation, and finally, patchy loss of sensibility.

It is concluded that in the territory of supply of any given nerve the site of onset and the spread of sensory loss is irregular rather than centripetal, and that the centripetal advance of sensory loss up the limb as a whole is due to the differences in the pressure exerted on the nerves supplying the hand and forearm respectively. There is no evidence to show that nerves become more susceptible to pressure in the intact human arm as they are traced proximally.

SPECHT, HEINZ (Bethesda, Md.). Some effects of changes in the density of respired gases on the velocity pattern of the breath.

Data on respiratory patterns obtained from subjects at ground level and at an atmospheric pressure equivalent to 30,000 ft. indicate that

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an increased velocity is induced by the change in density and that this facilitation of ventilation introduces or enhances pauses between the reciprocal phases of the breath. The effect is particularly marked following expiration and persists even in hyperventilation following heavy exercise. Theoretical implications include the normal distribution of breath pauses with respect to ventilative efficiency and the possibility of developing a method for making a quantitative estimate of such lung functions.

STERN, KURT G. (Brooklyn, New York). **On the isolation and properties of a native chromosomal nucleoprotein.**

A study of the protein system of calf thymus tissue by physical-chemical methods has revealed the presence of a number of cytoplasmic proteins, in addition to the desoxyribonucleoprotein forming the chief component of the cell nuclei. The cytoplasm contains several globulin-like proteins, soluble in 0.14 M. NaCl solution and precipitable by ammonium sulfate at concentrations ranging from 0.2 to 0.7 saturation, as well as appreciable amounts of ribose-nucleoprotein. The electrophoretic mobility of these cytoplasmic constituents is being studied in crude tissue extracts as well as in solutions of the various fractions purified by salting-out methods.

The chromosomal desoxyribonucleoprotein may be prepared either by extracting it directly from the disintegrated tissue with solvents of low ionic strength and subsequent purification by repeated precipitation at 0.14 M. NaCl concentration, or it may be isolated from the nuclear material remaining after exhaustive extraction of the cytoplasmic proteins with 0.14 M. NaCl. In either case the desoxyribonucleoprotein passes into solution slowly through a condensed and a dilute gel state. All operations are carried out at low temperature and in the presence of sodium arsenate to inhibit the activity of thymonucleodepolymerase.

The nucleoprotein isolated in this manner is electrophoretically and ultracentrifugally homogeneous. The fairly compact particles have a molecular weight of the order of one million as judged from their rate of sedimentation. Its solutions in solvents of low ionic strength possess a relatively low viscosity and show no appreciable

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double refraction of flow. In the gel state, the material is thixotropic and non-birefringent. In order to distinguish this native desoxy-ribonucleoprotein from artefacts, such as chromosin, which have suffered dissociation into free nucleic acid and histone through the use of strong salt solutions in their preparation, and as an indication of the probable close relationship of this material to the genes of the chromosomes, the name *Genoprotein T* (for thymus) is proposed for it.

VERNEY, E. B. (Cambridge). The osmotic release of post-pituitary antidiuretic substance.

When hypertonic solutions of NaCl are injected into the carotid artery of the dog during water diuresis an inhibition of urine secretion occurs, the magnitude of the response varying with the tonicity of the solution at constant rate and period of injection and with the period of the injection at constant volume and tonicity of solution. Hypertonic solutions of urea, however, are without action. The response to NaCl is of pituitary origin, seeing that it is diminished by some 90% following removal of the posterior lobe. When solutions of dextrose, sucrose, or Na_2SO_4 are injected, of such strength as will produce the same increase in osmotic pressure (O.P.) of the carotid blood as does the hypertonic solution of NaCl, the responses are quantitatively indistinguishable. The response, therefore, is of osmotic origin, and the term 'osmoreceptors' has been introduced as descriptive of the autonomic receptive elements with which the neurohypophysis is functionally linked.

When hypertonic solutions of NaCl or sucrose are infused into the carotid over a period of 10 min., in such circumstances that a local increase of some 4% in the O.P. of the blood is produced, the resultant release of post-pituitary antidiuretic substance is about $2.5 \mu\text{U}/\text{sec}$. With comparable solutions of dextrose, however, the resultant release is less and variable.

When the period of infusion of NaCl is extended to 40 min. and the local increase in O.P. of the blood is some 2% only, the urine flow gradually falls to and is maintained at a low resting value from which it slowly recovers when the infusion is stopped. Assay of such

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response shows it to be equivalent to that produced by the intravenous infusion of post-pituitary extract at $1 \mu\text{U}/\text{sec}$. Comparable intracarotid infusions of sucrose elicit responses which on assay give a closely similar value, but comparable infusions of dextrose are without apparent osmotic action.

It appears from these experiments that the osmoreceptors are freely permeable to urea, less freely permeable to dextrose, and relatively impermeable to sodium chloride and sucrose.

Water diuresis, then, may be fitly and accurately described as a condition of physiological diabetes insipidus, the antidiuretic secretion of the neurohypophysis being a hormone in the sense that its liberation is continuously governed by the concentration of chloride, and possibly of other osmotically active substances, in the arterial plasma.

WAKERLIN, G. E., DONALDSON, W., KAMM, O., MOSS, W. G.,
MINATOYA, H., LEFCO, T., MARSHALL, J., and WALKER, R.
(Chicago). **Treatment of experimental renal hypertension.**

Following earlier reports by our research group on the antihypertensive effect of daily intramuscular injections of crude hog renal extracts for four to six months in renal hypertensive dogs (*Spec. Pub. N. Y. Acad. Sc.*, 3, 117, 1946), we have continued work aimed at the fractionation, purification, and identification of the active principle of the crude extracts, as well as its mechanism of action. To date a total of twenty-five renal extract fractions have been studied for antihypertensive potency. Six of these have proved active but different lots of presumably the same fraction have varied considerably in potency. Our results suggest that one-kidney (unilaterally constricted, contralaterally nephrectomized) hypertensive dogs are somewhat more responsive to treatment than two-kidney (bilaterally constricted) dogs and that early renal hypertension is more amenable to treatment than late hypertension. Our observations indicate poor correlation between the renin content of our extract fractions and their hypertensive potency and between the antirenin serum titres and the antihypertensive responses of the dogs.

Our research group has also reported successful prophylaxis

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against experimental renal hypertension in dogs by means of daily intramuscular injections of crude renal extracts for four to six months, and the eventual development of hypertension in the successfully prophylacticated animals 3½ to 4 years after renal artery constriction and treatment. In further studies to produce maximum prophylaxis, elucidate the mechanism, and separate the active renal principle, we have used four renal extracts containing varying amounts of renin. Five of the twelve animals treated with these fractions were protected against experimental renal hypertension. One of the four extracts studied (all of which showed prophylactic activity) was free of renin. There was no correlation between anti-renin titres and prophylactic effect. Comparison with therapeutic effect in established hypertension indicated that prophylaxis is a more sensitive test for the antihypertensive renal principle than therapeutic assay. Further studies are under way.

WEDDELL, G., SINCLAIR, D., and FEINDEL, W. (Oxford). **The significance of multiple innervation of cutaneous pain 'spots' in relation to the quality of pain sensibility.**

1. It is well known that pain of an unpleasant quality can be elicited from certain cutaneous scars, and also from skin at the borders of areas which have either been recently denervated or are in the course of sensory recovery. Sensory tests have been carried out in several such cases, and the areas of skin concerned have subsequently been examined histologically after vital staining with methylene blue. It was found that in all cases where pain of an unpleasant quality could be aroused the nerve nets and terminals subserving pain were invariably isolated from their neighbours, in contrast to the interweaving which normally obtains.

On the other hand, the threshold recorded was found to be correlated with abnormalities in the morphology of the endings. The lowest thresholds occurred when the subjacent pain fibres were surmounted by growth cones ending just beneath the basal layer of the epidermis.

2. Direct stimulation of pain fibres in a human digital nerve has shown conclusively that such fibres obey the 'all or none' law. It

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follows that no modification of the characteristics of the stimulus applied to a single pain fibre will give rise to any change in the quality of the sensation perceived. From the observations reported in paragraph 1 it is suggested that changes in quality are due to alteration of the number and peripheral pattern of fibres involved in the conduction of impulses arising from a given stimulus.

3. Further support for this hypothesis has been provided by investigations of a different kind. Compression of the human arm by means of a sphygmomanometer cuff, at a tension exceeding systolic blood pressure, leads eventually to a loss of the various sensory modalities in the skin of the limb peripheral to the cuff. In such experiments, the first indication that pain sensibility is becoming affected is a change in quality of the sensation which can be aroused. It is suggested that there is a progressive irregular loss of function in the individual fibres supplying the terminal pain networks, and that the alteration in the quality of painful sensation occurs at a stage where the number of fibres supplying the network stimulated has become adequately reduced.

WEINER, J. S. (Oxford). Renal function of men working in hot environments.

When men carry out moderately hard work in environments at wet bulb temperatures above 90° F. they may, in a few hours, experience a marked degree of dehydration and salt deficiency, if these losses are not made good in the drinking water. Under these conditions the kidney is subject not only to the effects of water and salt loss but also to the circulatory changes associated with muscular work and profuse sweating. These circumstances provide a good opportunity to review experimentally some of the factors which are generally held to be concerned in the physiological control of urine formation.

Nude subjects exposed for 2½ hours to dry bulb temperature 100° F., wet bulb temperature 94° F., air movement about 50 ft./min., and carrying out step-climbing work, lose on the average 3 kgms. water and 14-18 gms. of NaCl in the sweat. When no water or salt is replaced (by drinking) there is a marked oliguria during and

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after the exposure. When the subject is kept in salt and water balance, by frequent administration of water, the urinary output during the period in the heat still remains at the previous low level, and is only slightly raised on leaving the room. Similarly, the maintenance of water balance or salt balance separately does not affect the urinary output during heat exposure; in the case of water replacement only is there a marked diuresis about an hour after leaving the heat.

The effect of a diuretic dose (750 cc.) of water given when the same grade and routine of work is performed in ordinary room conditions, is a prompt and large diuresis. A diuretic dose given in the heat, however, when no water or salt was administered, produced no effect on urinary output before or after heat exposure; when in salt and water balance, the diuretic dose increases the output only slightly. When water loss alone was replaced, the effect of a diuretic dose was again not marked during heat exposure, but resulted in a secondary diuresis after leaving the hot room. When salt only is replaced, the oliguria is present both during and after the heat exposure in spite of a diuretic dose.

There is also a reduction in salt loss in urine during and after heat exposure as compared to the urinary loss seen in experiments in cool conditions. This is not altogether due to reduction in urinary output. To some extent it appears to be due to a specific retention of chloride as suggested by the results of certain of the experimental series.

The above results lead to the conclusion that dehydration and salt deficiency, singly or together, are not essentially responsible for the oliguria and reduced urinary salt output of profusely sweating subjects. These features persist even when the water and salt loss in the sweat are fully replaced. Moreover, as long as the subject remains in the heat, the kidney is singularly unresponsive to the 'diuretic' stimuli of extra water or salt.

ADAIR, G. S. (Cambridge). A type of free energy with physiological applications.

The concept of free energy was introduced by *Helmholtz*. Chemical affinity and the maximum work obtainable in isothermal processes

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are determined by the free energy rather than the total internal energy.

The function A , called the Helmholtz free energy, is equal to $U - TS$, where U = internal energy, T = temperature, and S = entropy. The function G , called the Gibbs free energy, is equal to $U - TS + PV$, where P = pressure and V = volume. Both A and G are functions of n_a, n_b, n_c , the numbers of mols of the component substances designated a, b , and c .

It is here suggested that a third type of free energy, symbolized A_G and defined by formula (1) is applicable to systems of physiological interest, where the mol numbers n_a, n_b, \dots of substances that can diffuse across membranes—natural or artificial—are not independent variables but functions of the mol numbers of the non-diffusible substances and of the composition of the dialysate L_o which surrounds the membrane.

$$A_G = U - \sum_r (\partial U / \partial x_r^*) x_r^* = \sum_{n-r} (\partial U / \partial x_j) x_j. \quad (1)$$

x = an extensive variable—a variable directly proportional to the volume of the liquid, for example S, V, n_a, n_b, n_c . r (subscript) = number of extensive variables, e.g. x_r^* , that are functions of intensive variables. n (subscript) = total number of extensive variables. $n - r$ = number of extensive variables, e.g. x_j , that are independent variables.

The intensive variables include $T, -P$ and the chemical potentials μ_a, μ_b . $T = \partial U / \partial S, -P$ (or \bar{P}) = $\partial U / \partial V, \mu_a = \partial U / \partial n_a$.

Variations in μ_a can be controlled by membrane equilibria, since $d\mu_a = d\mu_a$ in fluid L_o , where $d\mu_a = RT d \log c_a$, if c_a be small. c_a = concentration.

It may be noted that A_G is the same as A if r be 1.0 and x_1^* be S . A_G differs from G in that $-P$ or \bar{P} is taken as an independent variable instead of $+P$.

The differential dA_G in equation (2) has a number of applications indicated in formulae (3) and (4).

$$A = (TdS \text{ or } -SdT) + (\bar{P}dV \text{ or } -Vd\bar{P}) + \sum \mu_i dn_i - \sum n_i^* d\mu_i; \quad (2)$$

or (in brackets) implies that TdS and $\bar{P}dV$ must be deleted if T and \bar{P} be the independent variables. μ_i = potential of a diffusible component, controlled by membrane equilibria or by a gas phase.

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Gibbs' definitions of the potentials and his criteria for equilibrium in terms of U , A , G , and the function $H = U + PV$ are summarized in formulae (3) and (4).

$$\partial A_G / \partial n_j = \mu_j, \quad (3)$$

$$\partial A_G / \partial \xi = 0. \quad (4)$$

ξ denotes the degree of advancement of a reversible reaction, a notation due to de Donder.¹

The late *Sir Joseph Barcroft*² emphasized the importance of the control of chemical variables in his discussion of *Claude Bernard's* statement: 'La fixité du milieu intérieur est la condition de la vie libre.' *Barcroft's* own work on the oxygen dissociation curves of blood at controlled tensions of carbon dioxide is an excellent example of a system in which the chemical potential of one component, CO_2 , is kept constant.

The differential coefficient ($\partial \log p_{\text{O}_2} / \partial \log p_{\text{CO}_2}$) or $\partial \mu_{\text{O}_2} / \partial \mu_{\text{CO}_2}$ for a constant concentration of free and combined oxygen can be derived from his curves and by formula (2) this coefficient is equal to

$$\partial^2 A_G / \partial \mu_{\text{CO}_2} \partial n_{\text{O}_2} \text{ or } -(\partial n_{\text{CO}_2} / \partial n_{\text{O}_2}),$$

the number of mols of carbon dioxide expelled per mol of oxygen combined at a constant tension of carbon dioxide p_{CO_2} .

¹ De Donder, Th., and Van Rysselberghe, P., London: Oxford Univ. Press (1936).

² Barcroft, J., *The Architecture of Physiological Function*. Cambridge (1934).

AHLMARK, A. (Stockholm). The histaminolytic power of plasma with special reference to pregnancy.

The plasma of man has, as a rule, little histaminolytic power, one ml. plasma of a healthy non-pregnant woman inactivating about 0.002 γ histamine base in one hour. In pathological cases and especially in pregnancy, however, there is a marked increase, which may reach values 5,000 times higher than in non-pregnant women. The characteristics of the histamine inactivating principle seem to be the same as those shown in histaminase or diamine oxidase.

The author gives a biological method for the quantitative determination of the histaminolytic power of plasma, partially based on Code's modification of *Barsoum's* and *Gaddum's* histamine deter-

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mination method. The histaminolytic power is expressed as the amount of histamine base, which under certain defined conditions is activated by 1 ml. plasma in 1 hour (γ /ml./h.).

Plasma from healthy non-pregnant women shows, as just mentioned, an average histaminolytic power of 0.002 γ /ml./h.: in two cases of gynecological and hormonal dysfunctions the author has found values of *ca.* 0.01 γ /ml./h. on repeated determinations. During the menstrual cycle there seems to be a minimum of histaminolytic power in the intermenstruum. In pregnant women the increase in the enzyme effect begins in about the seventh week after the last menstruation, i.e. *ca.* five weeks after the fecundation, and is particularly pronounced from the 8th to the 13th week, rising then 10–15% daily. This increase from one day to another can be shown by the method adopted. The histaminolytic power usually reaches a maximum during the 7th month of pregnancy, then sinks in some cases somewhat and rises slightly towards the end of the time.

The increase in the histaminolytic power between the 8th and the 13th weeks proceeds so similarly in different women that in healthy subjects it is possible in 2 cases out of 3 to state how far the pregnancy has gone to within *ca.* 6 days.

The author has studied the enzyme effect of plasma in various pathological conditions of pregnancy. Dr. T. Walentin has followed up about 500 cases of imminent abortions, extrauterine pregnancies, and hydatidiform mole. In imminent abortions with good prognosis the histaminolytic power of plasma is normal or almost normal (i.e. corresponding to the values found in healthy pregnancy), while in those in which the pregnancy is interrupted the enzyme effect is extremely low. In cases of extrauterine pregnancy the histaminolytic power is increased; in cases of hydatidiform mole, too, there are characteristic plasma values. The determination of the enzyme effect in the diseases just mentioned are of practical diagnostic and prognostic value. Cases of albuminuria and toxemia of pregnancy show normal, increased, or decreased values.

AROCHA, H. G., and DE VENANZI, F. (Caracas, Venezuela).

Rapid increase of plasma proteins induced by the injection of adrenocortical extract and the role played by the spleen in this process.

Intravenous injection of adreno-cortical extract in the dog under barbiturate anaesthesia produces a fast increase of total plasma proteins which reaches its maximum 15 minutes after the injection (+0.31 g. % average), maintains its value 30 minutes later (+0.29 g. %), and ultimately decreases. These results are statistically significant.

Hematocrit values are initially low in general and show great variability 15 and 30 minutes after the injection. The average of the 45 minute samples increased significantly; this increase is more marked in the dogs with lower initial values.

Twenty dogs were employed and an adrenocortical extract dosified according to the Meio Lewis technique was given intravenously to the animals. The total serum proteins were determined by Kagan's densimetric procedure.

The experiments were also carried out in seven human beings. Male subjects in good health were chosen and the same adrenocortical extract was given intravenously. The results show that the average for the 30 minute samples is the only definite high one. The increase is small (0.17 g. %), but it is, however, statistically significant.

The role played by the liver and spleen in the rapid increase of proteinaemia produced by adrenocortical extract given intravenously was studied in 14 dogs.

In order to exclude the liver from the general circulation in seven of these animals portocaval anastomoses were performed, tying the hepatic artery and the portal vessel behind the anastomosis. The spleen was removed in the other 7 dogs. The same adrenocortical extract was given intravenously to both groups of animals (liver excluded and splenectomized).

In all cases, 15, 30, 45, and 60 minutes after the injection the proteinaemia was determined. In the dogs with the liver excluded a rapid increase of total protein concentration was observed, reaching its maximum 30 minutes after the injection (+0.44 g. % average)

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and starting to decrease at 45 minutes. The hematocrit values showed a small hemodilution after the injection.

In the splenectomized dogs, the proteinaemia values were almost the same before and after the intravenous administration of the adreno-cortical extract. The hematocrit values showed also in these cases a slight hemodilution following injection. The results indicate that the spleen is the organ from which most of the proteins are mobilized by the action of the adrenal-cortex.

BARCROFT, H., and HAMILTON, G. T. C. (Cambridge). *Results of sympathectomy in man.*

Regeneration of sympathetic nerve fibres was first described by Langley. Lee found that sympathetic fibres in the cat regenerated more certainly than somatic ones. In man section of sympathetic nerves is a recognised form of treatment. Differences of opinion exist as to whether the divided fibres regenerate. The question is of importance both to human physiology and to surgery. This communication reports the results of testing nearly fifty sympathectomized arms for the presence of sympathetic fibres.

VON BÉKÉSY, GEORG (Stockholm). *Vibration pattern of the basilar membrane of the ear.*

An optical means of measuring phase relations in the cochlea is described. With the stapes set into sinusoidal vibration, the phase relations, measured along the length of the cochlear partition, show that a travelling wave has been set up. The form of resonance which appears does not correspond at all with that to be found in a simple vibrating system. Measurements are presented for a frequency of 200 c.p.s. of the amplitude and phase of vibration at various places along the cochlear partition. From these is derived a curve showing the longitudinal bending of the partition with the travelling wave at two different points in time.

Very small changes in the form of vibration can easily be demonstrated by the measurements of phase. By this means it is shown that the basilar membrane cannot be released from tension since it is not normally under tension. The elastic properties of the various

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distinguishable tissues within the cochlear partition were measured. These measurements show that only the elasticity of the basilar membrane changes through the length of the cochlear canal. The other portions of the partition are quite constant throughout the entire distance.

Further, the non-linearity in the vibration of the partition is investigated with results to indicate that the observed lowering of pitch of a tone when the loudness is increased cannot be produced by mechanical means.

BØE, JENS (Oslo). The methylenblue method for the determination of ascorbic acid in blood-serum.

The methylenblue method for the determination of ascorbic acid in blood-serum (*Martini and Bonsignore, Lund and Lieck*) has been subjected to severe criticism. As to the 2-6-dichlorophenol indophenol method one has not been quite as keen to criticise. The latter method has generally been accepted more or less without objections. When a solution of ascorbic acid is titrated with 2-6-dichlorophenol indophenol at pH below 2.2, one will find that the amount of the dye needed varies highly with the pH, because the colour of 2-6-dichlorophenol indophenol is fading rapidly without addition of ascorbic acid at pH's below 2.2, and the faster the more acid the solution.

The redox potentials of ascorbic acid and methylenblue lie very close together, while 2-6-dichlorophenol indophenol is a stronger oxydising agent. It will therefore also be reduced by a series of substances that do not reduce methylenblue. Methylenblue, therefore, should be a more specific indicator for the estimation of ascorbic acid than 2-6-dichlorophenol indophenol.

The reaction between ascorbic acid and methylenblue was therefore made subject of a thorough investigation, especially its dependency of the pH, the intensity of illumination, the temperature of the solution and contamination with small amounts of copper ions, hemoglobin and hemoglobin derivatives, &c. These experiments were repeated on deproteinised blood-serum filtrates, and it was shown that the course of the reaction under otherwise equal conditions was identical with that found with pure ascorbic acid solutions. In all

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these experiments a Pulfrich step photometer was used. The work of previous investigators on autoxidation of ascorbic acid in blood-serum and deproteinised filtrates was repeated and supplemented.

On the basis of the results obtained, a method for the determination of ascorbic acid in blood-serum is proposed. The principle of this method is the following:

Deproteinisation by metaphosphoric acid. The ascorbic acid present in the filtrate is determined by the reduction of methylenblue induced by intensive illumination at pH 2.3-2.5. Methylenblue is added in excess, and the decolorisation is followed during illumination in the Pulfrich photometer. For illumination a Philips cinema bulb (250 W., 230 v., 5500 int. lumen) is used, which is placed horizontally with its plane filament 7 cm. above the surface of the solution.

The method is demonstrated, and its accuracy discussed.

BOERI, E., and VESCIA, A. (Napoli). On the oxygenation of haemoglobin.

In 1936 *Hill* and *Wolvekamp* described the effect of dilution on the α_2 -affinity of whole blood. We have tried to analyse further this effect. Our experiments have been carried out on horse blood at pH 6.3 and 7.4, room temperature. The saturation has been measured by means of a photo-electric method, similar in principle to *Kramer's* method (1934); but the photo-electric current has been measured by the *Poggendorff's* compensation procedure, as proposed by *Gobler* (1945). Provided that the circuit magnitudes are carefully selected, the method is very accurate: on a 1 m. rheocord the index points to the saturation y on a logarithmic scale, ranging from $y = 0$ (hydrosulphite) to $y = 1$ (air). Particulars will be found in the article *in extenso*. As a measure of the α_2 -affinity the p_m value of the stoichiometric equation (Boeri, 1946) has been used. Following results are found. 1. On horse blood, pH = 6.3, $T = 16^\circ \text{C}$., the dilution effect begins and is complete at dilution respectively of 1/10 and 1/100. Values of p_m for dilutions 1/5, 1/10, 1/18, 1/25, 1/50, 1/100, 1/200 were, e.g., on a blood sample respectively 8.9, 8.9, 8.0, 7.8, 5.2, 4.7, 4.7. By plotting p_m against blood concentration an all or none concentration-action curve is obtained, suggesting

either a statistical or a successive stages effect. 2. At pH 6.3 a corpuscle suspension 1/100 shows an O_2 -affinity which is intermediate between those of two solutions of haemolyzed blood 1/10 and 1/100. We suspected that an 'inhibitor' was partially removed through the red cell membrane at this pH. But a 1/10 solution at pH 7.4 made from corpuscles formerly kept at pH 6.3 and then washed, re-suspended and haemolyzed, did not show, *ceteris paribus*, any increased O_2 -affinity. Besides this, the O_2 -affinity of a corpuscle suspension at pH 6.3 is independent of the corpuscle concentration. We are inclined to believe that the effect is due to pH differences between inside and outside the red cell membrane; a similar hypothesis was suggested by Root and Irving (1943) in order to explain the different effects of CO_2 on the affinity of whole and haemolyzed blood of *Tautoga onitis*. 3. Unlike the case of the respiration of sea urchin's sperm (Barron and Goldinger, 1941), 0.001 or 0.002 M iodoacetate is not an active substitute for dilution, since it has no action on the O_2 -affinity of a blood solution. This phenomenon is of some interest, since already Hill and Wolvekamp thought that the sulphydryl concentration could be responsible for the dilution effect. The researches are still in progress.

BONNET, V., et BREMER, F. (Brussels). Potentiels 'synaptiques' et potentiels rythmiques des centres nerveux.

Moelle lombosacrée, grenouille spinale non narcotisée, stimuli sur racine dorsale ou nerf afférent; enregistrements simultanés des potentiels 'synaptiques' dorsaux ou ventraux (dérivation 'électrotonique' radiculaire, ¹⁻⁶) et des potentiels 'spinaux' superficiels dorsaux (cf. ^{7, 8}) ou ventraux, ainsi que du myogramme réflexe isométrique.

Le potentiel 'synaptique' représente une réponse particulière de la cellule nerveuse ayant les caractères, à la fois d'une réaction protoplasmique et d'une modification subliminaire: graduable (additive, ²) mais par incréments en général plus petits que la réponse au premier stimulus (subnormalité post réactionnelle, ^{1, 3, 5, 6}); pouvant être déclenchée par addition latente d'influx cellulipètes (^{3, 4}). Dans le cas de deux stimuli réflexogènes successifs, la subnormalité post-réactionnelle des neurones ayant déjà répondu et le recrutement de

neurones additionnels conditionnent la grandeur de la réponse seconde.

Le potentiel 'spinal' dorsal en réponse à une volée afférente (cf. ^{7, 8}) a les caractères d'un 'spike' neuronique et représente la réaction propagée des interneurones. Il est précédé du potentiel des influx centripètes et coïncide avec la phase ascendante du potentiel synaptique enregistré électrotoniquement sur la racine dorsale correspondante. Une onde positive de même durée lui correspond à la face ventrale de la moelle. Potentiel synaptique dorsal et spike interneuronique varient parallèlement d'amplitude.

La facilitation (sommation) réflexe, s'exprimant par l'apparition d'une décharge centrifuge en réponse à un stimulus second, ne paraît pas être fonction simplement du degré de dépolarisation des motoneurones, mesuré par le niveau du potentiel 'synaptique' ventral (cf. ¹¹). L'admission du principe de cette relation causale permet toutefois une explication satisfaisante des données oscillographiques connues, y compris celles concernant le 'dorsal root reflex', ainsi que du fait qu'à l'afterdischarge du réflexe correspond une négativité soutenue de la racine antérieure, très semblable à celle que fait apparaître la vératrine. L'action caractéristique de cette substance sur les potentiels synaptiques dorsaux et ventraux (ralentissement extrême de leur décours) diffère de celle des convulsivants (strychnine, tubocurarine) et rappelle celle du poison sur le potentiel négatif tardif de la fibre nerveuse et du ganglion sympathique (^{9, 10}).

La strychnine à dose tétanisante rend régulièrement rythmiques les potentiels 'synaptiques' dorsaux et ventraux, dont les oscillations respectives se correspondent, avec un léger déphasage (antériorité des ventrales). Le processus convulsif paraît se résoudre électrophysiologiquement en une modification oscillatoire de la polarisation neuronique membranaire avec décharges cellulifuges correspondant aux phases négatives. L'action excitante (catélectrotonique) de celles-ci est vraisemblablement facilitée par la concomitance de variations rythmiques de l'excitabilité neuronique (cf. ^{12, 13}). Possibilité de l'application de cette donnée aux ondes centrales 'spontanées'.

¹ Barron et Matthews, *J. Physiol.* 92, 276 (1938). ² Fessard et Matthews, *J. Physiol.* 95, 39 P (1939). ³ Bremer, Bonnet, et Moldaver, *Arch. Internat. Physiol.* 52, 1 et 153 (1942). ⁴ Fessard, *C. R. Soc. Biol.* 138,

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446 (1944). ⁵ Eccles, *J. Neurophysiol.* 9, 87 (1946). ⁶ Eccles et Malcolm, *J. Neurophysiol.* 9, 139 (1946). ⁷ Gasser et Graham, *Am. J. Physiol.* 103, 303 (1933). ⁸ MacCouch, Hughes, et Stewart, *J. Neurophysiol.* 4, 547 (1941). ⁹ Rosenblueth et del Pozo, *Amer. J. Physiol.* 136, 699 (1942). ¹⁰ Lloyd, *J. Physiol.* 96, 118 (1939). ¹¹ Eccles, *J. Physiol.* 101, 465 (1942-3). ¹² Monnier et Coppée, *Arch. Internat. Physiol.* 48, 129 (1939). ¹³ Erlanger, Blair, et Schoepfle, *Am. J. Physiol.* 134, 705 (1941).

BREMER, F. (Brussels). Les Contractions secondaires, de forme vératrinique, du muscle squelettique.

Diversité des mécanismes mis en jeu dans les phénomènes de contraction secondaire du muscle squelettique. Trois types bien individualisés: la contraction vératrinique; la contraction secondaire, pseudo-vératrinique, provoquée par sommation de stimuli de très bref intervalle (*Bremer*¹); la contracture du muscle éseriné (*Feng*²; *Cowan*³).

Probabilité, dans le déterminisme de la contraction secondaire du muscle véatrinisé, de la synergie de divers facteurs.⁴ Parmi ceux-ci, importance de la phase d'excitabilité supernormale de la fibre musculaire associée au potentiel tardif négatif intensifié. Réalité de cette phase démontrée par l'exploration du seuil d'excitation du muscle véatrinisé et curarisé. Liaison probable du phénomène à l'effet contracturant de la succession de 2 stimuli, inefficaces isolément en cas d'intoxication légère. Grand intervalle optimum de ces stimuli.

Cette phase d'excitabilité supernormale fait défaut dans le cas de la contraction pseudo-véatrinique du muscle normal provoquée par répétition rapide (3 à 4 msec. d'intervalle) de 2 stimuli indirects ou directs, ceux-ci pouvant être appliqués sur le muscle curarisé ou atropinisé. Possibilité, grâce à la différence de leurs intervalles de sommation, de provoquer successivement sur le même gastrocnémien sensible de *Rana temporaria*, légèrement véatrinisé, les deux types de contraction secondaire.

Rôle d'un facteur chimique dans le déterminisme de la contraction pseudo-véatrinique, indiqué par son renforcement à la suite d'un bref tétanos initial et son affaiblissement après irrigation du muscle au Ringer. Absence d'effet de l'éserine et de la prostigmine. Action dépressive de la quinine et de l'anélectrotonus, renforçatrice du catélectrotonus. Effet paradoxal d'inhibition par un troisième

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stimulus (initial, précédant la paire de stimuli contracturants). Oscillogramme cathodique caractérisé par de très petites oscillations de potentiel se superposant à une négativité prolongée. Probabilité néanmoins d'un élément important de contracture vraie dans la contraction pseudo-vératrinique, indiqué par: (a) son abolition réversible par la chaleur (contrastant avec le renforcement de la vératrinique dans ces mêmes conditions); (b) la disparité de la tension contractile et du raccourcissement du muscle. Accentuation transitoire de la contraction pseudovératrinique à la suite de la dégénérescence wallérienne des fibres nerveuses motrices,⁵ nouvel argument pour son homologie, déjà suggérée¹ avec la myotonie.

L'intervalle optimum de 3 à 4 msec. des 2 stimuli directs ou indirects provoquant la contraction pseudo-vératrinique se retrouve dans différents autres phénomènes: sommation d'influx à la jonction neuromusculaire légèrement curarisée;⁶ contracture du muscle éseriné,² activité répétitive provoquée du muscle intoxiqué par le baryum.³ Il s'agit apparemment d'une caractéristique temporelle du tissu jonctionnel myoneural, persistant sur le muscle énérvé ou curarisé.

¹ Bremer, *J. Physiol.* 76, 65 (1932) ² Feng, *Chin. J. Physiol.* 11, 51 (1937). ³ Cowan, *Proc. Roy. Soc. B.* 129, 357 (1940). ⁴ Krayer et Acheson, *Physiol. Rev.* 26, 383 (1946). ⁵ De Smedt, observations non publiées. ⁶ Bremer, *C.R. Soc. Biol.* 97, 1174 (1927).

BUCHTHAL, F., DEUTSCH, A., KNAPPEIS, G. G., and MUNCH-PETERSEN, A. (Copenhagen). **Effects of adenosine triphosphate on myosin and muscle.**

The volume constriction of actomyosin threads (Szent Györgyi) under the influence of minute amounts of adenosine triphosphate (ATP) is independent of the enzymatic activity of the contractile protein. It is accompanied by a decrease in static and dynamic elasticity and has been interpreted as being due to the dissolution of approximately two thirds of the elastically active linkages. The production of a volume constriction in actomyosin threads is confined to ATP and thus highly specific in contrast to the increase in extensibility found by Engelhardt only in enzymatically active but non-contractile myosin threads. Inosine triphosphate (ITP) enhances the effect of

ATP, while acetylcholine and other phosphates such as creatine phosphate and different inorganic phosphates have an inhibiting effect. The inhibition is most pronounced with triphosphate and decreases with the number of phosphate groups in the molecule. The enzymatic activity of myosin solutions is less specific than the physical changes produced in myosin threads, as ITP and tripolyphosphate are also split enzymatically. Changes in flow-birefringence (*Needham*) are, however, confined to ATP and ITP, tripolyphosphate inhibiting the change in birefringence produced by ATP.

In striated amphibian and mammalian muscle ATP initiates a contraction (10^{-6} μ g.). This is a direct effect on the muscular substance. Of the other phosphates examined adenosine diphosphate (ADP), ITP, and tripolyphosphate have a similar action. The effect is hardly due to the removal of intracellular Ca as citrate only releases a contraction in considerably higher concentrations and does not alter the sensitivity to subsequent application of ATP. Thus the triphosphate part of the molecule is sufficient to initiate the contractile process. ATP and ADP furthermore cause a slowly reversible change in birefringence like that following electrical stimulation. A contraction produced by the other phosphates is not associated with a corresponding change in birefringence. Adenylic acid applied together with pyrophosphate or creatine phosphate acts like ATP possibly due to an intracellular synthesis of the latter. The changes in birefringence are considered an expression of certain restitutional processes in the protein molecule. They are inhibited by sulfhydryl reagents (mono-iodoacetic acid and porphyrexid), different phosphates, acetylcholine and denervation. Apart from the latter the same agents inhibit the volume constriction of myosin threads. In normal and curarised muscle ATP in subthreshold doses has a facilitating effect on subsequent stimulation. In denervated muscle previous application of acetylcholine blocks the stimulating effect of intra-arterially applied ATP (*Buchthal* and *Kahlson*), while the latter still acts when applied intramuscularly.

Our experiments on striated and smooth muscle and on the spinal cord indicate that ATP has a double action (1) a stimulating effect probably following its liberation from a complex compound by the nervous impulse initiating i.e. a discharge of the contractile protein and (2) the primary link in the transfer of energy for restitution, i.e.

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recharge of the protein molecule. Its trigger action is hardly connected with the enzymatic break-down of ATP as inhibition of ATPase does not impede the release of contraction. The mechanism of the transfer of energy liberated by the enzymatic break-down of ATP is still open to question.

CHANCE, BRITTON (Stockholm). The enzyme substrate compound in the oxidation of alcohols by catalase and hydrogen peroxide.

Keilin (1945)¹ has shown that strong catalase solutions may oxidize lower alcohols when catalase is coupled with various oxidative enzyme systems which produce H_2O_2 . The physiological importance of this function of catalase was difficult to evaluate since only indirect measurements of this type of catalase activity were possible. A sensitive and rapid spectrophotometric technique patterned after that of Hartridge and Roughton and Millikan (1936)¹ has revealed the existence of an intermediate compound in the reaction of catalase and hydrogen peroxide. Measurements of the acceleration of the small rate of disappearance of this intermediate by various alcohols give, for ethanol and methanol, second-order reaction velocity constants over a range from 1×10^{-4} to 1×10^{-1} M/L but at higher concentrations tend to a first-order reaction, a 'saturation' effect. The rate constants are 1000, 1000, 17, 2, and $0.1 \text{ L} \times \text{M}^{-1} \times \text{S}^{-1}$ for ethanol, methanol, n-propanol, n-butanol, and iso-pentanol respectively. Thus this enzyme-substrate compound has the properties required to explain Keilin's experiments; a graded activity towards lower alcohols and a turnover about ten times as great as was found in his experiments. This is a true peroxidatic reaction of catalase, hydrogen peroxide, and alcohols, which is in many respects very similar to the reaction of the primary peroxidase-hydrogen-peroxide compound with various acceptors.

Agner (1947)² has recently measured the kinetics of the disappearance of methanol from the blood of rabbits and has found the reaction to be first order with respect to the methanol concentration as the data above would require. The correlation of this activity with the peroxidatic activity of the known liver catalase content is excellent. If such correlation is not fortuitous, hydrogen peroxide must

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be present in the rabbit liver in a concentration approximately equal to the catalase concentration (1×10^{-6} M/L). Accumulation of a higher concentration would be prevented by the catalatic activity of this enzyme.

The properties of this intermediate compound of catalase and hydrogen peroxide are of great interest as an indicator of the mechanism of peroxidatic and catalatic reactions. The spectrum, molecular constitution, kinetics, equilibrium, and competitive inhibition by cyanide, azide and ethylhydroperoxide have been determined and show that, although the rate of formation of the compound (the most rapid enzyme reaction yet measured,

$$k_1 = 3 \times 10^7 \text{ L} \times \text{M}^{-1} \times \text{S}^{-1})$$

is sufficient to account for both types of activity, a special mechanism must be assumed to account for the nearly explosive catalytic reaction.

¹ Roughton, F. J. W., and Millikan, G. A., *Proc. Roy. Soc. London, Series A*, 155, 258 (1936). ² Agner, K., *Acta Physiologica* (1947) (in press). ³ Keilin, D., and Hartree, E. F., *Biochem. Jour.* 39, 293 (1945).

CROOKE, A. C., HENLY, A. A., and MORRIS, C. J. O. R. (London). Preparation and properties of ultrafilterable adrenotrophic hormone.

The ultrafiltration of the adrenotrophic hormone of the pituitary gland has previously been reported by *Anselmino and Hoffmann and Herold* (1934)¹ and by *Tyslowitz* (1943). However, no evidence is available as to the potency of such preparations relative to the homogeneous protein with adrenotrophic activity isolated by *Li, Simpson, and Evans* (1943)² and by *Sayers, White, and Long* (1943).⁴ Indeed *Tyslowitz's*³ material appears to be less active than his starting material.

During 1938-9 we had prepared by ultrafiltration of pituitary extracts, material such that 200 μ g. would produce a 50% increase in adrenal weight in the hypophysectomised rat. The method of assay used was a modification of that of *Crooke and Gilmour* (1938).² Male rats of 90-110 gm. body weight are hypophysectomised, and after 12-18 days used for assay. Confirmation of completeness of hypophysectomy is obtained from testis weights at autopsy. Groups

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of four animals are injected twice daily for 3 days, and killed on the fourth day. Adrenal and testis weights are then determined. A 100% increase in adrenal weight over hypophysectomised controls is arbitrarily taken as one unit.

This material was therefore considerably more potent than the protein preparation of *Sayers, et al.* (1943),⁴ which required a dosage level of 5 mg. to produce a comparable effect. At this time, however, it was very difficult to obtain reproducible results. It has now been found that both pH and ionic strength of the solution are important during the process of ultrafiltration, and by working at pH 3.9 and ionic strength $\mu = 0.1$, it is possible consistently to obtain ultrafiltrates of high potency. The membranes used have a pore size of about 15 Å, so that it is extremely unlikely that the hormone can have a molecular weight greater than 3,000, as contrasted with 20,000 for the protein preparations of the American workers. The ultrafilterable hormone is probably polypeptide in nature, since the activity is completely destroyed by papain digestion. It is stable for 1 hr. at 100° C. at pH 1.0, and unlike the preparations of *Li, et al.* (1943)³ is unaffected by trichloroacetic acid.

The question whether the protein hormone or the polypeptide hormone is the physiologically active principle of the pituitary gland remains to be settled by further experiment.

¹ Anselmino, K. J., Hoffmann, F., and Herold, L., *Klin. Wchnschr.* 13, 209 (1934).

² Crooke, A. C., and Gilmour, J. R., *J. Path. Bact.* 47, 525 (1938).

³ Li, C. H., Evans, H. M., and Simpson, M. E., *J. Biol. Chem.* 149, 413 (1943).

⁴ Sayers, G., White, A., and Long, C. H. N., *ibid.*, 425 (1943).

⁵ Tyslowitz, R., *Science*, 98, 225 (1943).

DOLIVO, M., et PETITPIERRE, CL. (Lausanne). L'Activité électrophysiologique d'un nerf après son interruption.

Les essais ont été effectués principalement sur le nerf phrénique. L'interruption a été réalisée par section au moyen de ciseaux, par coagulation sans interruption anatomique du nerf, par action pharmacologique ou par le froid. Ces différents modes de section ont donné des résultats pratiquement identiques:

La première interruption entraîne toujours une augmentation des courants d'action, donc de l'activité modulée du nerf sectionné et également une augmentation des courants d'action de l'autre nerf

phrénique. Parfois cette première section provoque une activité permanente, donc non modulée, pouvant masquer complètement les courants d'action. Cette activité permanente ne se constate que du côté sectionné et peut apparaître même si le nerf est préalablement isolé du centre. Une section ultérieure ne provoque une augmentation des courants d'action que si elle a lieu à moins de 2 cm. d'une électrode de dérivation. Ces sections ultérieures n'entraînent pas de modifications de l'activité du phrénique opposé. Parfois l'activité permanente n'apparaît qu'à l'occasion de l'une de ces deuxième ou troisième sections. Ces interruptions ultérieures peuvent faire disparaître instantanément une activité permanente apparue lors d'une première section.

Des essais identiques effectués sur les nerfs largynés supérieurs ont confirmé les résultats obtenus sur le phrénique.

Les réponses différentes aux sections successives d'un même nerf montrent que les augmentations constatées n'ont certainement pas toutes la même origine.

DUBUISSON, M. (Liège). Myosines α et β dans les muscles normaux, fatigués et contracturés.

On peut, à partir de muscles striés, préparer deux myosines différentes: la myosine d'*Edsall* (courte extraction: $\frac{1}{2}$ à 1 heure) et la myosine B de *Szent-Györgyi* (longue extraction: 6 à 10 heures, ou plus). Des recherches électrophorétiques ont montré que ces deux myosines sont constituées de trois composantes, que nous avons appelées myosines α , β et γ , dans des proportions différentes. La myosine d'*Edsall* contient: 25% d' α , 70% de β , 5% de γ et l'actomyosine: de 80 à 90% de α , 5 à 15% de β et 5% de γ .¹

Nous avons réussi à isoler les myosines α et β par précipitation au sulfate d'ammonium (état pur à l'électrophorèse).² Tandis que les solutions de myosine α sont très turbides, très biréfringentes à l'écoulement, très visqueuses et solubles, au pH 7.00, à $\mu > 0.5$, celles de myosine β sont limpides, peu visqueuses, pratiquement dépourvues de biréfringence et solubles, au pH 7.00, à des forces ioniques moindres. Ces différences de solubilité permettent de séparer aisément les deux myosines, par un ajustement convenable de la force ionique et du pH, sans devoir faire appel à la méthode de 'salting-

out¹. La méthode, mise au point dans notre laboratoire par Hamoir, permet de procéder, dans les extraits musculaires, à une évaluation quantitative des taux de myosine α et β beaucoup plus rapidement que ne le permet la méthode électrophorétique.

La myosine α résulte d'une transformation progressive, au cours de l'extraction, de la myosine β . Elle représente probablement l'actomyosine proprement dite de *Szent-Györgi*, tandis que la myosine β correspondrait à la myosine A de cet auteur.

Les myosines extraites de muscles fatigués, chez le lapin, sont caractérisées par l'absence des composantes α et γ .¹ Jacob a montré en outre, dans notre laboratoire, que les extraits de muscles fatigués contiennent une moindre quantité de myosine β que ceux des muscles normaux; par contre, dans les muscles contracturés par l'acide monobromacétique, les extraits, très pauvres en myosine β , contiennent une certaine quantité de myosine α .

Ces différences montrent la grande complexité du problème et font penser que les deux myosines principales α et β , réversiblement transformables l'une dans l'autre, pourraient constituer les supports principaux des deux mécanismes antagonistes: la contraction et la décontraction, qui correspondent à deux processus actifs, le premier lié au métabolisme de l'A.T.P., le second, au métabolisme du phosphagène.²

¹ M. Dubuisson, *Experientia* 2, 7 (1946).

² Id., ib. 2, 10 (1946).

³ Id., ib., sous presse.

DUGAL, L.-P., and THÉRIEN, M. (Laval, Quebec). Ascorbic acid and adaptation to cold temperatures.

The authors wanted to prove their hypothesis (based on their observation that a large increase of ascorbic acid is found in the tissues of rats, when the latter are exposed to cold temperatures and adapted, as indicated by the growth curves) that among possible factors, ascorbic acid in large doses is necessary for resistance and adaptation to cold temperatures, in animals like guinea-pigs and man relying on exogenous sources of that vitamin.

With guinea-pigs exposed to cold temperatures and receiving daily by oral administration, 0.5 mg., 1 mg., 2 mgs., 2.5 mgs., 5.0 mgs., 7.5 mgs., 10 mgs., 25 mgs., and 75 mgs. respectively (each lot sub-

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divided into two groups, one exposed to cold and the other kept at room temperature), they have obtained the following results:

(a) *Resistance and Adaptation* (as measured by weight curves) to cold temperatures is a direct function of the amount of ascorbic acid received daily.

In other words, all groups behave the same way and well at room temperature, but differences appear between groups as the temperature is lowered, the only group being capable of adaptation at the lowest temperature used (-8°C.) being the one receiving the most ascorbic acid daily (75 mgs.).

(b) *Resistance and adaptation* to cold temperatures is a direct function of the ascorbic acid level in the tissues, especially in the adrenals.

(c) *Animals about to die* (at cold temperatures) have much less ascorbic acid in their adrenals than control animals kept at room temperature.

(d) Not only does the relation between ascorbic acid levels in the adrenals and adaptation to cold hold for groups receiving the different doses mentioned, but there is a strong indication that the same relation holds for all individuals within a group, during the process of acclimatization.

(e) There is also a serious indication that more ascorbic acid is retained in the adrenals of the guinea-pigs kept at cold temperatures, during the first weeks of exposure (Resistance) than in the adrenals of control animals of the same age, receiving the same amount of ascorbic acid daily, but kept at room temperature.

(f) The amount of food ingested daily increases at cold temperatures, but is the same for all groups studied, whatever the quantity of ascorbic acid may be for each group. The ascorbic acid being given by mouth independently of the diet, the daily quantity ingested is constant for a given group.

V. EULER, U. S., and LILJESTRAND, G. (Stockholm). *Circulatory and respiratory regulation factors in muscular work.*

During moderate muscular work the blood-pressure level is only little affected in spite of the greatly increased cardiac output and concomitant vascular changes. In order to obtain information on the regulatory forces, experiments were performed on cats and dogs

under chloralose anaesthesia, subjected to muscular work by electrical stimulation of the hind legs. During the work the blood-pressure remained unchanged after a small transient fall, even after section of the spinal cord at L 1. After elimination of the sinus and aortic regulatory mechanisms muscular work was accompanied by a strong fall in pressure, indicating that these mechanisms are normally engaged. The result also implies a rise in sympathetic vasomotor and cardiac tone during work. In some instances the blood-pressure reached a higher level after termination of the work, especially when the animal was allowed to breathe gas mixtures rich in carbon dioxide, poor in oxygen, or both.

A study of the effect on the blood-pressure of various gas mixtures in the respired air confirmed that high percentages of carbon dioxide produced a strong rise in pressure in the resting cat even after exclusion of the sinus and aortic mechanisms, whereas oxygen lack caused a fall. Small doses of ergotamine (0.1–0.2 mg./kg.) which reverse the effect of CO₂ on the blood-pressure, presumably by blocking the vasomotor centre to CO₂, also cause a much stronger fall in pressure during muscular work on deregulated animals, and abolish the secondary rise. The latter may therefore depend on a factor having similar effects on the vasomotor centre as carbon dioxide.

Many attempts have been made to find satisfactory explanations for the remarkable adjustment of the ventilation to the metabolic needs. Since it seemed reasonable to allot some influence to the chemosensitive mechanisms of the carotid and aortic bodies, the effect of muscular work on respiration before and after exclusion of these bodies was studied in cats and dogs, anaesthetized with chloralose. A moderate reduction of the ventilation per volume oxygen consumed was found, showing that though probably some effect is exerted by these mechanisms, they do not represent the chief factor. Reflex actions from the working muscles could be excluded since it was shown that section of the nervous paths from the limbs did not appreciably alter the response.

The results obtained are in favour of the conception that the regulatory forces are ultimately determined by the composition of the blood, though the direct influence may be governed by the actual state of the respiratory centre as postulated by *Winterstein* and *Gesell*.

v. EULER, U. S., and LILJESTRAND, G. (Stockholm). **Studies on the pulmonary arterial blood-pressure.**

It has been demonstrated by numerous workers that the systemic arterial blood-pressure is regulated through reflexes evoked by stimulation of baroreceptors and chemoreceptors as well as through direct action of the blood on the vasomotor centre. It seemed of interest to investigate whether similar influences are exercised on the pulmonary arterial blood-pressure.

Experiments were performed on cats under chloralose anaesthesia, a special cannula according to Mellin being inserted in the wall of the pulmonary artery. It was connected with a vertical narrow glass tube filled with Ringer solution and the pressure recorded with a piston recorder. In most cases the thorax of the animal was closed and spontaneous respiration restored.

Clamping of the common carotids elicited the usual rise in the systemic pressure, but had hardly any influence on the pulmonary arterial pressure. Occlusion of the left lung artery led to a rise of about 20%; moderate muscular work induced by electrical stimulation caused an increase of about 30% in the pulmonary arterial pressure. Section of the vagi did not influence these results.

Breathing of pure oxygen lowered the pulmonary arterial pressure and oxygen-lack raised it without notably influencing the pressure in the left auricle. A mixture of carbon dioxide (6.5–20%) and oxygen raised the pressure slightly. Neither vagotomy nor extirpation of the stellate ganglia had any influence on the effect produced by oxygen or oxygen want on the arterial blood-pressure. The same held true, as found recently by Logaras, for ergotaminisation or atropinisation of the animal.

It is concluded that alterations in the oxygen pressure in the alveoli have a direct influence on the pulmonary vessels, an increased pressure leading to a dilatation and a reduction to a contraction. By this mechanism an adequate distribution of the blood through the various parts of the lungs, according to the efficiency of aeration, is enabled. The results also seem to have some bearing on such questions as the therapeutic application of oxygen, its toxic effects, the influence of oxygen pressure on vital capacity, atelectasis, &c.

FLEISCH, A. (Lausanne). Impulsions nerveuses afférentes dans les racines antérieures du nerf phrénique.

L'introduction ou l'enlèvement brusque d'une résistance dans le trajet respiratoire déclenche des réflexes proprioceptifs au niveau de la musculature respiratoire. Il a été montré de façon indubitable que ces réflexes sont contrôlés par le centre respiratoire, en particulier leur déclenchement provoque une modification de l'amplitude des courants d'action du nerf phrénique. Or ces réflexes persistent après la section de toutes les voies afférentes respiratoires connues, à savoir: les racines postérieures cervicales, la moelle à la limite cervico-dorsale, les nerfs vagues et sympathiques dans le cou et les ganglions stellaires. Donc le centre respiratoire peut percevoir ce qui se passe à la périphérie, bien qu'il n'y soit plus relié que par un nerf moteur, le phrénique.

D'autres faits le prouvent encore: chez l'animal privé de toutes voies afférentes apparaissent assez fréquemment des mouvements rapides d'inspiration et d'expiration qui disparaissent dès que l'on introduit la résistance et réapparaissent dès qu'on la supprime. Sur l'oscillogramme du nerf phrénique, ces mouvements rapides se marquent par des courants d'action moteurs.

De plus, la section d'un phrénique entraîne une augmentation immédiate des courants d'action de l'autre nerf phrénique, ceci de nouveau toutes voies afférentes sectionnées. Enfin un fait encore prouve que des impulsions centripètes peuvent remonter le long du nerf phrénique et le long des racines antérieures de la moelle: l'introduction d'une résistance dans les voies respiratoires supérieures entraîne un ralentissement du rythme respiratoire. Ce ralentissement est moins prononcé si les nerfs vagues sont coupés, mais il ne disparaît entièrement que si la totalité des fibres du phrénique, et non seulement les racines postérieures de ce nerf, sont sectionnées.

Les racines antérieures du nerf phrénique ne sont donc pas purement motrices, mais contiennent des fibres capables de conduire des afférences régulatrices de la respiration.

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FRAZER, A. C., FRENCH, J. M., and SAGROTT, P. E. (Birmingham). **The mechanism of fat absorption.**

Triglycerides are partially hydrolysed in the intestinal lumen.¹ The extent of hydrolysis is influenced by the nature of the triglyceride, the pH of the environment, the enzyme/substrate ratio, and possibly by alteration in the normal sequence of absorptive changes. Fine emulsification occurs due to the triple system monoglyceride/fatty acid/bile salts.²

The fatty material passes through the outer membrane of the intestinal cell as water soluble compounds, or as fine particles. Normal electrolyte metabolism may be important for particulate absorption. The effect of adrenalectomy on fat absorption may be due to the consequent disturbance in electrolyte metabolism.³

Phosphorylation occurs in the intestinal cell.^{4,5} The administration of choline facilitates the passage of fat through the inner membrane of the intestinal cell into the corium of the villus.⁶ The mechanism of this action and the effect of mono-iodo-acetic acid and phloridzin on fat absorption will be discussed.

Fat may be distributed after absorption, either by the portal vein to the liver, or by the thoracic duct to the systemic blood. Fat absorbed in particulate form normally passes by the lymphatic route, while material absorbed as water soluble compounds mainly passes into the portal circulation.⁷

¹ Frazer, A. C., and Sammons, H. G., *Biochem. Jour.* 39, 122 (1945).

² Frazer, A. C., Schulman, J. H., and Stewart, H. C., *J. Physiol.* 103, 306 (1944).

³ Frazer, A. C., *Physiol. Rev.* 26, 103 (1946).

⁴ Sinclair, R. G., *J. Biol. Chem.* 115, 211 (1936).

⁵ Schmidt-Nielsen, K., *Acta. Soc. Physiol. Scand. (D.)* 12, suppl. 37 (1946).

⁶ Frazer, A. C., *Nature*, London, 157, 414 (1946).

⁷ Frazer, A. C., *J. Physiol.* 102, 306 (1943).

GLAVIND, JOHS. (Copenhagen). **The clotting of crustacean blood.**

Many invertebrates have no coagulation of the blood in the proper sense involving the plasma, but another mechanism which is rather highly developed, namely the agglutination of the blood-cells. Thereby a pseudo-clot is formed, which with respect to elasticity, compactness, and retractability resembles very much a fibrin clot, and probably has the same significance in hemostasis. Outside the

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vertebrates true blood coagulation occurs only in the arthropodes, especially the Crustacea. Since the investigations of *P. Nolf* in 1909, and in a period of great progress in the field of mammalian blood coagulation, very little has been published on blood clotting in invertebrates. A summary of the results of the author's studies in crustacean blood-clotting is given below.

Crustacean and mammalian blood-clotting show great differences, and no enzyme active in one of the systems is active in the other. The most important characteristic feature of crustacean blood-clotting is the fact that it occurs in *one* phase only for which the presence of calcium-ions is necessary. The phase consists in the conversion of a dissolved protein, crustacea-fibrinogen into a gel, crustacea-fibrin. The process is accelerated by an enzyme, crustacea-koagulin. Crustacea-koagulin resembles thromboplastin in several of its properties, in others thrombin. It resembles thromboplastin in its occurrence in the blood-cells, muscles, &c., and in the requirement of calcium-ions for activity, but not with respect to physical-chemical properties. With respect to these it rather resembles thrombin, but differs from it in not requiring calcium-ions for activity, in its distribution and in not being produced from a pro-enzyme. Aqueous solutions of crustacea-koagulin must be stored at low temperatures, under CO₂-ice for instance. Crustacea-fibrinogen and -fibrin resemble the corresponding vertebrate substances, but the crustacea-fibrin-clot shows considerably less elasticity and strength. Crustacea-fibrinogen has an iso-electric point about pH 4.1. The clotting of crustacean blood is inhibited by heparin and hirudin, but large amounts are required. Crustacea-koagulin from lobsters is active against fibrinogen from all the species examined including the cray-fish which live in fresh water.

It should be mentioned that it is beyond doubt that in crustacean hemostasis the agglutination of the blood-cells plays a role of its own which cannot be looked upon as secondary to the blood-clotting. This fact should be considered by workers in human blood-clotting, where also the function of the platelets in hemostasis may not only be explained from their role as a thromboplastin source.

GORDON, G., and HOLBOURN, A. H. S. (Oxford). **The contraction-wave in small areas of active muscle.**

As an electrical action potential travels along a muscle fibre, it is accompanied by a wave of mechanical change. These events have been studied by simultaneous electrical and mechanical recording from the small muscles of the face (e.g. *M. orbicularis oculi*) in man.

The mechanical change consists of a local contraction of the muscle fibre in an active region, and is recorded by electro-mechanical apparatus capable of detecting movements at right-angles to the long axis of the muscle. The mechanical change and the electrical action potential from the same motor unit are both recorded through the skin.

Preliminary measurements from our records suggest that the beginning of the mechanical change occurs about 2 msec. after the beginning of the electrical action potential. During a maximal voluntary contraction, when the rate of firing in a motor unit may reach 50 impulses per second, the mechanical changes detected by our recording system remain discrete and unaltered in size, and each wave returns to its resting base-line. The apparatus which we have used so far has had a short time-constant, and it is doubtful if we could have observed any appreciable rise in the mechanical base-line during a tetanus.

The mechanical changes may be detected by the ear without amplification other than that provided by a suitable 'stethoscope'. Undoubtedly they cause the discrete sounds, at regular rhythms, which the ear may detect by bone conduction when such muscles as the masseter are undergoing tonic or phasic contraction.

GRANDJEAN, E. (Lausanne). **The functions of the cerebrospinal-nervous-system in high mountains.**

The effect of altitude upon diverse nervous functions has been the object of our research performed at the scientific station of Jungfrauoch (3,450 m.) and in the valley. Some new mechanical apparatuses^{1,2} were devised for quantitative measurement of excitability and efficiency of various sensory functions, the knee-jerk reflex and reaction time. In addition we have done research on the

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effects of pure oxygen inhalation at high altitude and of artificial oxygen deficiency at low levels. The action of sympatho-mimetic and parasympatho-mimetic substances was the object of another series of experiments.

Results:

1. The high altitude (3,450 m.) lowered the threshold of tactile sensitivity of the skin and cornea.
2. It lowered the threshold of gustatory sensitivity.
3. It lowered the amplitude of equilibrio-static movements; this we have attributed to the increased efficiency of the sensory functions.
4. It amplified the knee-jerk reflex, manifested by a lowering of the threshold and an increase in the intensity of reflexes.
5. It lowered the reaction time to luminous stimulation.

All these modifications appeared during the stay at high altitude and disappeared only after the return to a low level. Taken together, these results show a stimulation of the cerebrospinal-nervous-system, which is thus in a state of increased reactivity provoked by the high altitude. These symptoms point toward ergotropism of the human organism.

6. At a high altitude the administration of pure oxygen rapidly produced a decrease in tactile sensitivity and the knee-jerk reflex. This shows that the diminution of a partial pressure of oxygen constitutes a primary factor which at high altitude is responsible for stimulation of nerve functions.

7. At a lower level the subjects who were submitted to an artificial oxygen deficiency (13.5% O_2 = partial pressure of O_2 at 3,500 m.) showed the same increase of tactile sensitivity and knee-jerk reflex as normally shown at the high altitude. However, during the first hour of oxygen deficiency a transitory inhibition of the knee-jerk reflex was observed. The transient character of this inhibition explains the contradiction between our results obtained in the mountains and those obtained by experimenters in aviation medicine working with the decompression chamber.^{3, 4, 5}

8. Our pharmacodynamic experiments have shown that adrenalin (0.5 mg.) stimulates tactile sensitivity and the knee-jerk reflex, whereas acetylcholine (0.1 g.) inhibits them. These results confirm our supposition that stimulation of the cerebrospinal-nervous-system at high altitude is due to a sympathetic erethism.

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¹ Fleisch, A., *Helv. Physiol. Acta*, 3, 355 (1945). ² Grandjean, E., *Helv. Physiol. Acta*, suppl. iv (1947). ³ Strughold, H., *Luftfahrtmed.* 2, 21c (1938). ⁴ Jokl, E., *J. Roy. Army Med. Corps*, 73, 289 (1939). ⁵ Roger, H., *La Presse med.* 85-6, 1521 (1939).

HARRIS, LESLIE J. (Cambridge). **Methods of assessing nutritional status in specific vitamins.**

For experimental animals it is generally recognized that intakes of nutrients sufficient to prevent symptoms of classical deficiency disease may still be inadequate, e.g. for optimal growth, healing of wounds, normal calcification, &c. For man the need still remains to develop further the methods by which status in specific nutrients may be determined, and more especially to devise *functional* tests to detect minor degrees of deficiency.

The following survey of methods relates to experiences at the Nutritional Laboratory, Cambridge.

Vitamin C: loading test. The past level of intake can be deducted from the number of days of standardized test-dosing needed to bring about 'saturation' (large overflow into urine).^{1, 2} In standardization measurements continued over 4 successive years, groups of boys have been kept on known graded intakes, and their responses tested at the end of each year. Past intakes of about 50-75 mg. give responses on the first day of test dosing, of about 30 mg. (L.o.N. standard) not later than second to third day, and so on in proportion with smaller intakes, until with cases of developed scurvy 7-10 days are needed.³ The method of test does not involve any presumption whether saturation is necessarily desirable or otherwise. Factors such as individual variation, and the presence of non-specific reducing substances in the 'resting urine', are not to be regarded as serious sources of error. The requirement in fevers or infection (notably phthisis) is greatly increased.³

Vitamin B₁: (a) loading test. Similarly the response to test doses of B₁ is graded in proportion to the past intake, but the test is quantitatively less sensitive than that for vitamin C.⁴

(b) Pyruvate-tolerance test. After doses of lactic acid (in rats) or glucose (in man), the form of the B.B.S. or pyruvate curve in urine or blood reflects the vitamin-B₁ status of the individual.⁵

Nicotinamide. The recommended procedure is to give test doses

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of nicotinamide by mouth and measure urinary excretion of methylated derivatives: analyses of blood for nicotinic acid or its products is unsatisfactory for the purpose.⁶

Vitamin A. (1) The vitamin-A economy can be influenced⁷ by the concurrent intake of other nutrients, acting either as inhibitors or protectors, and this may account for apparent discrepancies in the literature, e.g. in rates of depletion and time taken to produce signs of deficiency in man.⁸ (2) The dark-adaptation test for indicating incipient deficiency may be misleading unless appropriate apparatus is used, and unless the results are adequately checked, e.g. by double control (no improvement without dosing, improvement after dosing). (3) Determination of the reserves of vitamin A in the liver *post mortem* is useful for comparing trends in populations and in social groups, and the influence of disease.⁹

¹ Harris and Ray, *Lancet*, 1, 71 (1935); Harris and Abbasy, *ibid.* 2, 1429 (1937). ² Harris, *ibid.* 1, 642 (1942); 1, 515 (1943). ³ Abbasy, Harris, and Ellman, *ibid.* 2, 181 (1937); Harris, Passmore, and Pagel, *ibid.* 2, 183 (1937).

⁴ Harris and Leong, *ibid.* 1, 886 (1936); Wang and Yudkin, *Biochem. Jour.* 34, 343 (1940); Harris and Wang, *ibid.* 35, 1068 (1941); Wang and Harris, *Brit. Med. Jour.* 2, 451 (1943). ⁵ Banerji and Harris, *Biochem. Jour.* 33, 1346 (1939); Shils, Day, and McCollum, *J. Biol. Chem.* 139, 145 (1941); Bueding, Stein, and Wortis, *ibid.* 140, 697 (1941); Williams, Mason, and Wilder, *J. Nutr.* 25, 71 (1943).

⁶ Harris and Raymond, *Biochem. Jour.* 33, 2037 (1939); Kodicek and Wang, *Nature*, Lond. 148, 23 (1941); Najjar and Holt, *Science*, 93, 20 (1941); Ellinger, Glock, and Platt, *Biochem. Jour.* 36, proc. xi (1942); Wang and Kodicek, *ibid.* 37, 530 (1943); Huff and Perlzweig, *J. Biol. Chem.* 150, 395 (1943). ⁷ Moore, *Biochem. Jour.* 34, 1321 (1940). ⁸ Hecht and Mandelbaum, *J.A.M.A.* 112, 1910 (1939); Medical Research Council, Vitamin-A Sub-committee, *Nature*, Lond. 156, 11 (1945).

⁹ Moore, *Biochem. J.* 31, 155 (1937).

HEYMANS, C. (Ghent). Influence of di-isopropyl-fluorophosphate on the revival of nerve centers and nerve endings following acute anemia.

It has been shown in previous publications¹ that the respiratory, vasomotor, and heart vagus-sympathetic centers may revive after prolonged interrupting of perfusion, for periods as long as thirty minutes of complete arrest of circulation.

In the present group of experiments, the completely isolated head of a dog was perfused by a second dog. The perfused head was kept in connexion with the heart of his trunk (under artificial respiration)

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by means of the cervical vagus-sympathetic nerves alone. The activity of the respiratory center of the head was manifested by the respiratory movements of the larynx and nares. The activity of the cardio-regulatory vagal and sympathetic centers was noted by the heart rate of the trunk. It has been observed that the injection of di-isopropyl-fluorophosphate (D.F.P.) into the circulation of the isolated head, increases very much the resistance of the respiratory and cardiac vagal and sympathetic centers to acute anemia. When perfusion was re-established to the isolated head, the respiratory and cardiac vagal and sympathetic centers could in fact be revived and resume their activity even after a complete interruption of perfusion up to 90 minutes' duration.

The resistance of the sympathetic pupillary nerve endings to acute anemia was also tested. Stimulation of the cervical sympathetic nerve still induces mydriasis during the arrest of perfusion of the head up to 45 minutes. When perfusion was re-established, the mydriasis induced by sympathetic stimulation reappears very soon, even after a complete interruption of perfusion up to 120 minutes' duration.

¹ Heymans, C., and Ladon, A., *C. R. Soc. Biol.* **90**, 93 (1924). Heymans, C., Jourdan, F., and Nowak, Stanley J. G., *ibid.* **117**, 470 (1934). Heymans, C., Bouckaert, J. J., Jourdan, F., Nowak, Stanley J. G., and Farber, Sidney, *Arch. of Neurol. a. Psychiat.* **38**, 304 (1937). Heymans, C., and Bouckaert, J. J., *C. R. Soc. Biol.* **119**, 324 (1935). *Summaries of Commun.*, xvth Intern. Physiol. Congr., Moscow, 1935, p. 156. *Bull. Acad. Roy. Méd. Belg.*, p. 29 (1938).

HEYMANS, C., and JACOB, J. (Ghent). On the pharmacology of di-isopropyl-fluorophosphate (D.F.P.).

The observation of Mackworth (March 1942), Adrian, Feldberg, and Kilby (Nov. 1942), Mazur and Bodansky (*J. Biol. Chem.* **163**, 261 (1946)), Koelle and Gilman (*J. of Pharmacol. Exper. Therap.* **87**, 421, 435 (1946)) that di-isopropyl-fluorophosphate (D.F.P.) inhibits the cholinesterases activity of blood and tissues, has been amply corroborated by others. In previous publications (C. Heymans, *Experientia*, **2**, 260 (1946); C. Heymans, R. Pannier, and R. Verbeke, *Proc. Soc. Exp. Biol. and Med.* **62**, 228 (1946); *Arch. int. pharmacodyn.* **72**, 405 (1946)) it has been shown in dogs that D.F.P., injected in doses

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which inhibit deeply or completely the cholinesterases activity of blood serum, red blood cells, and tissues, does not sensitize the response of the heart to vagal stimulation and does not affect the cardio-vascular and respiratory responses to carotid sinus stimulation.

In the present study it has been observed that intravenous injection of high doses D.F.P. (5-6 mg./kg.) in non-anaesthetized dogs or in dogs anaesthetized with chloralose may induce unrest, convulsions, muscular fasciculations, bronchospasm, hyperperistalsis, and bladder contraction, but no change in heart rate or increase of blood pressure, although the cholinesterases of blood, heart, and brain were deeply or completely inhibited. Still higher doses D.F.P. slow the heart, but the heart vagal junctions are then blocked; this bradycardia persists after bilateral vagotomy. Atropine suppresses bronchospasm, hyperperistalsis, bladder contraction, and bradycardia, but not the convulsions and the muscular fasciculations. Nembutal decreases or suppresses the convulsions and the muscular fasciculations. After atropine, D.F.P. still does not produce a rise of blood pressure. Muscular twitchings caused by D.F.P. persist in acutely denervated or excised striated muscles, but do not occur after axon degeneration. The characteristic response of the innervated or actually denervated muscle to eserine is the same after as before destruction of muscle cholinesterase by D.F.P.

Injection of D.F.P. into the isolated perfused head of dogs does not increase the direct or reflex (carotid sinus or aortic pressoreceptors stimulation) excitability of the cardio-inhibitory vagal and respiratory centers, although the cholinesterase activity of the brain was deeply or completely inactivated.

These and previous observations are not in favour of a role of cholinesterases in the transmission of the nervous stimulations which have been tested. Experimental data suggest that in addition to the cholinesterase inhibiting activity, D.F.P., prostigmine and eserine exert also other pharmacological actions.

HERXHEIMER, H. (London). The heart rate in recovery from severe exercise.

A number of authors (Lythgoe and Pereira (1925),¹ Schneider and Crampton (1936),² Barman, Consolazio, and Moreiro (1942))³ have

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observed that recovery of the heart rate lasts longer than other essential factors of recovery, for instance O_2 intake and cardiac output. Grill (1934)⁴ has found in some of his plethysmographic experiments that the blood flow in the forearm increased after the cessation of exercise. If this peripheral dilatation is the reason for the persistent tachycardia after severe exercise, it should be possible to prevent both by bandaging legs and arms.

Peddalling on a standing bicycle for 5 minutes at rate of 60/min. with a maximum load which led to exhaustion within that period, was used as test exercise. Four trained boys between 16 and 18 years acted as subjects. Immediately after the exercise they lay down and had their arms and legs from wrists and ankles up to the axils and groins enclosed in a thin rubber bandage. The pressure of the bandage constricted the limb slightly, causing slight venous congestion of hands and feet and (sometimes) transient pins and needles. The pulse was counted before exercise and during the recovery till it reached its basal value. Ten experiments with bandages and 10 controls were carried out. When bandages were used, the pulse rate returned to normal after 22-53 minutes, in the controls after 59-77 minutes (with one exception when it returned after 40 minutes). This result, details of which are given in the figure, shows that there is a definite influence of bandaging. It is in good agreement with the X-ray observation that the heart silhouette becomes smaller after hard exercise and remains so for a long time, and with the observations of Mateeff (1935)³ and others. These found that quiet standing after severe exercise led to fainting which could be prevented by bandaging the legs.

² Barman, Consolazio, and Moreiro, *Am. J. Physiol.* 138, 16 (1942). ⁴ Grill, *Skand. Arch. Physiol.* 67, 1 (1934). ¹ Lythgoe and Pereira, *Proc. Roy. Soc. B.* 98, 468 (1925). ³ Mateeff, *Arbeitsphysiol.* 8 (1935). ² Schneider, E., and Crampton, *Am. J. Physiol.* 117, 577 (1936).

HOLLANDER, F., and LAUBER, F. U. (New York). Comparison of eugenol with other stimuli for gastric mucus secretion.

Of various stimuli investigated in this laboratory for studying gastric mucus secretion, 5% clove oil-water emulsion was most effective. Optimal stimulating action was indicated by high viscosity, opacity, columnar cell content, pH, and volume of secretion after one applica-

tion of stimulus; also, by the failure to stimulate the acid secreting cells. However, clove oil is a mixture of several compounds—including about 80% eugenol (4-allyl-2 methoxy phenol). Hence, we have investigated pure eugenol as a topical stimulus for gastric mucus.

As in previous studies, fasting dogs with Heidenhain (corpus) pouches were used. 'Spontaneous' secretion was collected until its pH rose above 6.0, thus ensuring the absence of obvious parietal secretion. Then, about 50 ml. of an aqueous emulsion of eugenol (0.25, 0.5, 1.0, 2.0, or 5.0%) was introduced into the pouch through a mushroom catheter and held there for 15 minutes. Following its removal, collection of mucus by our usual technique was started. The time interval for each specimen varied according to its volume; the experiment was continued until the secretory rate became negligible.

The characteristics of mucus obtained with eugenol were qualitatively the same as with clove oil, aqueous ether solution, alcohol, gentle mucosal massage, &c. Some specimens were fluid; others jelly-like or of intermediate consistency. Some were transparent or translucent; others opaque. Some were cell-free or contained only cellular detritus; others contained many columnar cells—singly and in palisades. Leucocytes were frequently present. As with other stimuli, increasing viscosity, opacity, and columnar cell content are directly correlated statistically. This affords further evidence that pure mucus is colorless, transparent, of variable consistency, and cell-free, opacity being caused by desquamated cells and coagulated mucin.

The pH-values (glass electrode) of 224 specimens were 6.05–9.22. For 5% eugenol alone, the range was 7.53–9.22 and the mean 8.50 (S.D. = 0.28, 78 specimens), whereas for 5% clove oil the range was 7.28–8.47 and the mean 8.07 (S.D. = 0.31, 28 specimens). Mean values for the other stimuli were lower. Data on volume of mucus secreted after single applications of eugenol are being analyzed statistically; cursory examination indicates they are higher than for all the other stimuli.

It may be concluded that eugenol is an effective stimulus for gastric mucus secretion, and has the advantage over clove oil of being a pure chemical individual.

JACOBSON, W., and GOOD, P. M. (Cambridge). Observations on the nature of the anti-pernicious anaemia factor.

The anti-pernicious anaemia factor was first demonstrated in the liver, and later it was shown that the stomach, small and large intestines, had the same haemopoietic effect in cases of pernicious anaemia. The presence of this factor in the alimentary canal can be correlated with the distribution of the argentaffine cells in the mucosa. These cells are markedly reduced in pernicious anaemia. Very little was known about the chemical nature of the anti-pernicious anaemia factor prior to the synthesis of folic acid. Most of the known vitamins, many amino acids and other substances were isolated from liver extract, but none of these had the therapeutic action of the unknown factor.

The granules of the argentaffine cells were found to contain a pterin compound. As these cells appear to be connected with the elaboration of the anti-pernicious anaemia factor, it seemed possible that active liver extracts might contain a similar compound. Work on the fluorescence spectra of many liver extracts proved this to be the case and it was found that the intensity of the fluorescence spectrum of this pterin-containing compound in the liver extracts corresponded with the clinical activity of the extract. Work on folic acid—also a pterin compound—supports the idea that pterins are involved in haemopoiesis.

Folic acid, however, does not appear to be identical with the active liver principle because 100 mg. of folic acid are required to produce the same effect as about 1 to 8 mg. of liver extracts. Since folic acid is only present in insignificant amounts in highly active liver extracts, an attempt was made to determine the relation between these two haemopoietic factors. In the course of this work an enzyme has been prepared which oxidises xanthopterin to leucopterin. The distribution of this enzyme in animal tissue is being investigated.

Folic acid in concentration of 1 mg./ml. was incubated with a solution of the enzyme preparation. The incubated material was injected into cases of pernicious anaemia and produced a maximum response in the patients. Such a result could not be explained by the folic acid content of the fluid injected (3–4 ml.). It is suggested that folic acid has been converted into a compound of greater haemopoietic activity or into the anti-pernicious anaemia factor.

JALAVISTO, EEVA (Helsinki). The phantom limb phenomenon and some sensory physiological observations on 178 upper arm amputees.

An attempt to analyse the nature (peripheral neuro-somatic, neuro-vegetative, or central cortical) of different phenomenal features of the phantom limb.

From a statistical point of view, the symptomatology of the arm stump and of the phantom phenomenon show it to be improbable that any of the symptoms would be decidedly more important than any other for the production of a certain phenomenal character of the phantom. A quite distinct correlation ($P > 0.27\%$) was, however, found to exist between the following symptoms: shortening of the phantom, a constant or intermittent feeling of heaviness in the phantom and a cramping pain. This finding was interpreted as showing that all these symptoms may be somehow connected with an abnormal functioning of the proprioceptive system.

Some parts of the limb, especially the peripheral ones, are more accurately and more often represented in the phantom than others. The percentage values of the patients' statements, that a part is felt more accurately than others, agree with the relative extension of the sensory cortical areas representing the corresponding parts of the body as determined by Penfield and Boldrey in experiments with electrical excitation of the sensory cortex on conscious patients. If, correspondingly, the relative frequency of *spontaneous movements* perceived in the different joints of the phantom is compared with the relative extension of *motor* cortical areas, from which a certain movement may be evoked by electrical stimulation, a striking conformity seems to exist.

When these statistical results are combined with individual observations, the following interpretation concerning the nature of the phantom phenomenon seems best to fit in with the facts.

A phantom sensation may be evoked by different peripheral irritative symptoms, whether neuro-somatic or -vegetative is thereby of no importance. The completeness of the phantom as well as the accuracy with which a part of it is perceived depends not only on the pattern of peripheral impulsation, but also to a great extent upon the functional organisation of the sensory cortex. Correspondingly

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the functional structure of the motor cortex governs the motor phenomena perceived in the phantom.

A predominance of the left hemisphere probably accounts for a difference in phantom sensation between left and right, the right hand phantom being more often perceived as a complete limb, of natural size, feeling cold or warm, &c.

JOHNSON, J. RAYMOND (Brooklyn, N.Y.). **Analysis of the pressure gradient in the wall of the left ventricle.**

The fact that the intramyocardial pressure curve recorded from the wall of the left ventricle does not follow the contour of the intraventricular pressure curve, indicates that a straight line gradient of pressure from the endocardial to the epicardial surface of the heart wall does not obtain throughout the cardiac cycle. Experiments have been carried out to analyze the factors responsible for changes in the shape of this pressure gradient and to deduce the nature of these changes.

Since the contours of the intramyocardial and intraventricular pressure curves are similar during isometric contraction and approach similarity again toward the end of systole, it may probably be correctly assumed that all isometric phases of contraction produce even, straight line pressure gradients in the ventricular wall. This is supported by observations during increased resistance to ejection of blood from the heart as during clamping of the aorta. When the abdominal aorta is clamped the intramyocardial pressure curve assumes a shape resembling that of an intraventricular pressure curve. If the clamp is applied to the proximal aorta the similarity is still more striking and the entire contraction period becomes nearly isometric in nature.

During the period of rapid ejection of blood from the heart, the contours of the two curves differ considerably, indicating a changing form of the pressure gradient in the wall. If venous return is increased the rapidity of ejection is augmented and the difference in contours becomes more striking. The gradient of pressure must change then as the heart muscle alters its shape and position during active contraction and ejection of blood. The more rapid the muscular movements, the greater the influence on the pressure gradient.

These changes become more clearly understandable if one interprets intramyocardial pressure at any particular moment and at any particular depth as being produced by one layer of muscle contracting against another layer which in turn is contracting away from the first. During any isometric period of contraction the compression pressure between muscle layers at a given depth in the heart wall must be closely proportional to the thickness of the outside layer. During ejection of blood the inside layers are contracting away from the outside layers and intramyocardial pressure may actually decrease at a time when intraventricular pressure is rising. Such conditions would favor a more rapid intramural flow of coronary blood throughout most of the heart muscle.

LASER, H. (Cambridge). Isolation of a haemolytic substance from animal tissues and some of its properties.

The existence of a haemolytic substance in the blood has long been assumed, especially from consideration of diseases showing abnormal destruction of erythrocytes, when the amount of the lytic substance circulating in the blood was believed to be increased. *Morgenroth* and *Korschun* (1902)¹ and *Friedemann* (1909)² obtained an ether-soluble haemolytic principle from alcoholic extracts of several organs, as e.g. pancreas and gastric mucosa. *Bergenheim* and *Filthraeus* (1936)³ claim to have demonstrated the existence in blood plasma of a lysolecithin produced by a lecithinase which they believe to be present in the blood.

A substance which is strongly haemolytic *in vitro* has been isolated in crystalline form from human blood plasma (*Laser* and *Friedmann*, 1945).⁴ It contains only C, H, and O, being free from N and P. This definitely excludes its lecithin nature. It has so far been characterized as a monocarboxylic branched unsaturated fatty acid. Besides occurring in the blood plasma it is widely distributed in the animal body, brain especially giving a very high yield. Its natural inhibitors are proteins, mainly albumin; to a lesser extent globulins and calcium. The rate of haemolysis *in vitro* is considerably increased in presence of free haematin which is capable of counteracting the inhibition by proteins. This haematin activation of haemolysis does

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also apply to haemolysis by other substances, as, for example, bile salts and some detergents, but not to saponin.

¹ Berghem, B., and Fähræus, R., *Z. ges. exp. Med.* **97**, 555 (1936). ² Friedemann, U., *Arch. f. Hyg.* **69**, 105 (1909). ³ Korschun, S., and Morgenroth, J., *Berl. Kl. Wo.* **39**, 870 (1902). ⁴ Laser, H., and Friedmann, E., *Nature*, **156**, 507 (1945).

LEGGE, J. W., NICHOLSON, P., and ROUGHTON, F. J. W. (Cambridge). **Some studies of the kinetics of sheep haemoglobin in solution and in the red cell.**

I. The rates of CO uptake by haemoglobin in solution and in red cell suspensions have been measured by the Hartridge-Roughton-Millikan rapid reaction technique. The rate is 1.8–3 times slower in the suspensions. This retardation is attributed to the limiting effects of diffusion through the cell membrane and through the finite thickness of the cell interior. Theoretical maxima and minima solutions have previously been obtained for diffusion and chemical reaction through a slab of haemoglobin of thickness equal to that of the red cell, and these were close enough to fix the true solution fairly well over a considerable range. (F. J. W. Roughton, *Proc. Roy. Soc. B.* **111**, 1, 1932). No allowance was, however, made for the cell membrane. It was further assumed that the kinetics of the chemical reactions are the same for haemoglobin in the red cell as in solution. This is supported by the observation that reactions which are so slow that diffusion is not a limiting factor, proceed at the same rate in the cell and in solution. In the present work this assumption is retained and special numerical methods, developed during the war in connexion with heat transmission, are used to obtain accurate solutions, not only for the simple slab but also for the slab enclosed by a membrane of any assigned permeability.

In the case of $\text{CO} + \text{Hb} \rightarrow \text{COHb}$ and slower reactions, the time to half saturation varies linearly with $1/(\text{permeability of the membrane})$, while in the case of $\text{O}_2 + \text{Hb} \rightarrow \text{O}_2\text{Hb}$ and faster reactions there is some departure from linearity. By comparing the mathematical results and the observed rate of saturation of haemoglobin in the cell the membrane permeability can be estimated. If the thickness of the membrane is of the order 10^{-6} cm. (cf. electrical and other estimates) the value for the membrane diffusion coefficient is

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about 1/300 of that found for water. The mathematical method is a general one and is capable of further application to other non-steady state processes in biology.

II. In haemoglobin solutions the initial rate of association or dissociation is found to be unaffected by partial saturation of the haemoglobin with CO or O₂. At pH 10 the dissociation of O₂Hb goes smoothly to completion, but at pH 6.8 the reaction proceeds in two phases, the last quarter of the oxygen being dissociated far more slowly. This confirms an earlier result (F. J. W. Roughton, *Proc. Roy. Soc. B*, 115, 495, 1934) and may well be of considerable chemical and biological interest.

NASSET, E. S., and HEGGENESS, F. W. (Rochester, N.Y.). Concentration of enterocrinin, a chemical excitant for the glands of the small intestine.

A method for the preparation of enterocrinin was reported from this laboratory by R. M. Fink in 1943 (*Am. J. Physiol.* 139, 633) which gave a very potent product. The yield, however, was only about 6% of the original material. The present paper describes a much simpler method which yields 8 to 10 times as much enterocrinin as the earlier method. The first 6 or 8 feet of the small intestine of swine is turned inside out, washed in tap water, and extracted twice for an hour with 0.03 N HCl in 85% ethyl alcohol (1.5 liters/kg.). The combined alcoholic filtrates are concentrated to 1/250 of the original volume at reduced pressure and temperature. The sludge is removed by centrifugation and discarded. The supernatant liquid is considered as containing 100% of the enterocrinin and the threshold dose is 8 to 13 mg. of organic solids given intravenously to a dog. This solution is further concentrated to a thick syrup and extracted four times with methyl alcohol (7 ml. absolute/gm. organic solids). Soluble in methyl alcohol are 60 to 64% of the organic solids and 78 to 83% of the enterocrinin. The threshold dose is 6 to 10 mg. The dry methyl alcohol soluble material is dissolved in water and an aqueous solution of flavianic acid added (0.8 gm./1.0 gm. organic matter) and allowed to stand in the cold overnight. The flavianate is dissolved in water (80-90° C.) made slightly alkaline and the flavianic acid removed as the barium salt. Excess barium is removed as the sulfate. The

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flavianic acid reduces the organic matter to 10-17% of the original but retains 54 to 69% of the enterocrinin. The threshold dose is 2.0 to 2.5 mg. To this material in aqueous solution is added phosphotungstic acid (10% solution) to the point of complete precipitation (0.7 gm./1.0 gm. organic matter). The phosphotungstate is dissolved in alkaline solution (pH 8-10) and the phosphotungstic acid removed with barium. After removing excess barium the solution is extracted with butyl alcohol to remove traces of flavianic acid which may color the solution yellow. The phosphotungstic acid precipitation reduces the organic solids to 2-4% of the original but retains 54-58% of the enterocrinin. The threshold dose is 0.32-0.96 mg. This material still contains some secretin and vaso-depressor substances.

QUILLIAM, J. P. (London). The sensitization of the heart to acetyl choline by di-isopropyl fluorophosphonate, D.F.P.

Di-isopropyl fluorophosphonate, D.F.P., was shown by *Adrian, et al.* (1942)¹ to have a powerful and prolonged miotic action, to be lethal to animals in small doses and to inhibit cholinesterase in a manner somewhat similar to eserine. With these considerations in mind, a series of experiments was carried out to study the action of D.F.P. upon the mammalian heart (*Quilliam and Strong, 1947*)² with a view to using the substance in experimental work where a pronounced and long-lasting eserine-like effect might be required.

The isolated perfused rabbit heart was used. It was found that the injection of 5 to 25 mg. of pure D.F.P. caused a complete inhibition of cardiac activity which may be followed by a very gradual resumption of the beat but the amplitude rarely attained its previous height. With 0.25 to 2.5 mg. of D.F.P. the heart usually responded with a transient inhibition followed by a return to its previous vigour. This inhibition was unaffected by atropine in concentrations that blocked the action of acetyl choline.

The activity of acetyl choline after fluorization of the heart was much increased. It was found that if a certain dose of acetyl choline had an effect before D.F.P., then this effect was markedly potentiated after D.F.P. With full fluorization there was an increase in sensitivity to acetyl choline from up to 10 to 100 fold if the duration

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of cessation of cardiac activity followed by recovery be used as a measure for comparison. These changes appeared to be rapid in onset and permanent, but were not fully developed with lower dosages of D.F.P.

These effects were similar to those produced by the action of eserine on the heart but differ in that they occur fully developed very shortly after a single injection of D.F.P.; they seemed to be permanent and were more easily obtained than with eserine. After fluorization of the heart eserization leads not to a further increase in sensitivity to acetyl choline but often to a marked decrease in sensitivity to the latter drug. Thus it would seem that eserine affords some protection to the fluorized heart to the action of acetyl choline. This protection can be removed by prolonged perfusion with normal Ringer-Locke solution.

Increases in sensitivity to acetyl choline have been found after fluorizing with D.F.P. the isolated frog heart and the isolated frog rectus abdominis preparations (*Claydon* and *Quilliam*, unpublished observation). Upon the isolated rat phrenic nerve-diaphragm preparation D.F.P. exerts a prostigmine-like effect. (*Quilliam*, unpublished observation.)

¹ Adrian, E. A., Feldberg, W., and Kilby, B. A., 1942, quoted *Nature*, **158**, 625 (1946). ² Quilliam, J. P., and Strong, F. G., 1947 (unpublished observations).

KLUTZ, A., and ROSKAM, J. (Liège). Sympatholytic agents and average bleeding time after sympathectomy.

Sympathetic denervation (*Roskam*, 1938) as well as sympatholytic agents—including diethylamino-ethyl-benzodioxan, or 883 F (*Derouaux*, 1941)—increase the average bleeding time (A.B.T.).

In a few unpublished experiments, *Derouaux* observed that 883 F still increases the A.B.T. measured on the ear of rabbits which have been deprived of their superior cervical ganglia 15 days ago. He found, however, that the A.B.T. may be shortened instead, if 883 F is given 25 days after sympathectomy.

Using the method of *Roskam* and *Pauwen* (1937), we systematically studied this phenomenon. The following facts were observed after administration of 883 F to rabbits, at various intervals after removal of the superior cervical ganglia:

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1. The A.B.T. is shortened by 883 F during the first week.
2. At the end of the first week, the haemostatic action of the sympatholytic agent starts decreasing and finally vanishes on about the sixteenth day.
3. On the eighteenth day, 883 F, on the contrary, increases the A.B.T.
4. Toward the twenty-third day, or even earlier, 883 F becomes, once more, inactive with respect to the A.B.T.
5. On the thirty-first day and, also, at the end of the sixth and of the tenth week, 883 F again shortens the A.B.T. of a denervated ear, just as it does during the first week following the operation.

Similar results were obtained with ergotamin.

We cannot venture to propose any explanation for this queer behaviour.

Summary: Regional sympathectomy inverts the increasing action of a sympatholytic agent, 883 F, on the average bleeding time, except in the course of a period extending approximately over the third and the fourth week after denervation. During that period, 883 F either does not influence or, as it does in a normal animal, hinders the spontaneous arrest of haemorrhage. Qualitatively, the results obtained with ergotamin are similar.

Derouaux, G., *Arch. Internat. Pharmacodyn.* **66**, 231 (1941). Roskam, J.,
Arch. Internat. Physiol. **47**, 325 (1938). Roskam, J., and Pauwen, L., *Arch.*
Internat. Pharmacodyn. **57**, 450 (1937).

DEVENANZI, F., and GARCIA AROCHA, H. (Caracas, Venezuela).

Some physiological indexes of the inhabitants of Caracas especially related to the nutritional status.

The 'Instituto de Medicina Experimental' has met with the requirement of establishing local standards of normality that can be used to interpret correctly pathological data. Especially important in this regard are the physiological and biochemical data pertaining to the nutritional status, which is so influenced by the food-pattern of the region. The values found differ very much from the ones established in other countries and this is why their quotation seems to be of interest.

In 533 children¹ classified in five groups according to the economical level the values for total plasma proteins were in direct relation-

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ship with the income. In 405 adults¹ the total plasma proteins average was 6.58 gm. %, the mode 6.51-6.75, and 9.6% of the people had values of less than 6 gm. %. At the end of pregnancy² the average in 90 women was 5.91 gm. %, the mode being 5.49-6.25. At the beginning of lactation³ in 60 women, the average was 5.73 gm. % and the mode 5.75-6.00. The daily total nitrogen in the urine has been determined⁴ in 194 people. The average was 8.03 gm. \pm 2.80 (s) and the mode 6-7. 95% of the population was under 12 gm. %. The daily elimination of preformed creatinine was studied in 207 people;⁵ the average being 802 mgm. \pm 212 (s) and the mode 600-700. The elimination was smaller in the female, even expressing the results in terms of body-surface. The preformed creatinine in plasma was determined in 201 subjects;⁶ the average found was 1.36 mgm. % and the mode 1.41-1.60.

Vitamin A and carotene⁷ in blood-serum were determined in 200 people. Vitamin A average was 77 I.U. % and the mode 41-50. 78.5% of the people were under 100 I.U. The average for carotene was 125 I.U. with a mode of 101-120.

Dark adaptation was found to be low in most of 60 apparently normal subjects, and a relationship between it and the milk consumption was established. In the Venezuelan food-pattern the milk seems to be the most important source of Vitamin A.

The Vitamin C in the serum was determined in 200 people.⁸ The average concentration was 0.43 ± 0.51 (s) mg. % and the mode 0.30-0.40; 83% of the individuals were under 0.7 mgm. %.

The basal metabolic rate was established⁹ in 100 subjects and the values were found to be somewhat lower than the Dubois standards.

The alkaline reserve¹⁰ was studied in 100 individuals. The average was $52\% \pm 4.7$ and the mode 54-56. The decreased values found are probably related to the altitude at which Caracas is located.

¹ Garcia Arocha, H., *Anales Inst. Med. Exp.* 1, 81 (1942).

F., *Rev. Ministerio Sanidad y Asist. Soc.* 7, 847 (1942).

² *Tesis Doctoral Universidad Central de Venezuela*, 1943.

³ *Rev. Ministerio Sanidad y Asist. Soc.* 10, 251 (1945).

⁴ *Anales Inst. Med. Exp.* 2, 103 (1943-4).

⁵ *Exp.* 2, 5 (1943-4).

⁶ *DeVenanzi, F., Anales Inst. Med. Exp.*, in press.

⁷ *DeVenanzi, F., Anales Inst. Med. Exp.*, in press.

⁸ *DeVenanzi, F., Anales Inst. Med. Exp.*, in press.

⁹ *DeVenanzi, F., Anales Inst. Med. Exp.*, in press.

¹⁰ *Garcia Arocha, H., y Soto-Rivera, A., Anales Inst. Med. Exp.*, in press.

¹¹ *Guevara, J., Tesis Doctoral Universidad Central de Venezuela*, 1946.

¹ DeVenanzi,

² Cartaya, J. A.,

³ DeVenanzi, F.,

⁴ DeVenanzi, F.,

⁵ DeVenanzi, F.,

⁶ Boada, J. C.,

⁷ *Anales Inst. Med. Exp.*, in press.

⁸ *DeVenanzi, F.,*

⁹ *Anales Inst. Med. Exp.*, in press.

¹⁰ *Garcia Arocha, H., y Soto-Rivera, A.,*

¹¹ *Guevara, J., Tesis Doctoral*

VENNING, ELEANOR H., and BROWNE, J. S. L. (Montreal).

A study of adrenal function in man following damage.

It has been shown that following non-specific damage the adrenal of experimental animals hypertrophies.

In collaboration with metabolic studies on protein metabolism, an investigation has been carried out on the response of the adrenal in man to acute trauma such as burns, fractures, wounds, infections, and operations. For this purpose a method has been developed whereby small amounts of biologically active adrenal cortical steroids can be measured. It is dependent upon the deposition of glycogen in the livers of adrenalectomized mice. This method has been applied to the study of the urinary excretion of adrenal cortical-like substances in man under various conditions. These substances have been called glycogenic corticoids. In addition another group of adrenal metabolites, the 17-ketosteroids, have also been followed in the same cases.

When a healthy well-nourished individual is subjected to an acute trauma, such as a fracture or burn, &c., there is an immediate and rapid increase in the excretion of the glycogenic corticoids in the urine, reaching a maximum in most cases within 3 to 5 days. This elevated output is maintained for a varying period of time, depending to some extent upon the severity of the damage inflicted. In most cases the corticoid excretion is back to normal level by the end of the third week, but in several cases the increased excretion of corticoids is maintained for a much longer period. In some of the cases studied values around 400 units have been found at the peak of the excretion although generally the values lie between 200 and 300 units. The average excretion for males is 60 units per 24 hours. One unit is equivalent to the biological activity of one microgram of 17-OH 11 dehydro corticosterone. There is also usually an immediate rise in 17-ketosteroids, but this increase is not always maintained and the levels of excretion of these two groups of adrenal metabolites do not always parallel one another.

There is a marked difference in the behaviour of the previously healthy individual and the chronically ill or malnourished patient subjected to acute trauma. In the latter case, there may be either no increase in output of glycogenic corticoids or else the increase occurs

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for only a few days and is not sustained, reaching normal levels again by the end of the first week after injury. This failure of the adrenal to respond to damage in the debilitated person is also reflected in a decreased nitrogen metabolism in these individuals following the trauma.

WIERSMA, C. A. G. (Pasadena, Calif.). **Time relations of synaptic facilitation in the crayfish.**

As shown in an earlier investigation¹ a number of different single preganglionic fibers can be prepared in the central nervous system of the crayfish (*Cambarus clarkii*), stimulation of which results in discharge of the same postganglionic fibers. In the present experiments, the potentials obtained from a third root of an abdominal ganglion on stimulation of any two of the four giant fibers were used. In addition, stimulation of each giant was combined with that of a first root of the same ganglion and on the same side as the third root. First root stimulation with single shocks results in activation of the same efferent fibers excited by the giant fibers. For these experiments the preparations were all brought into a state in which a single impulse in any of the preganglionic pathways no longer resulted in a potential in the root used. This can be accomplished either by letting the preparation age or by stimulating a preganglionic fiber temporarily at high frequency. Subsequently the presence or absence of a root potential was noted on the second of two closely spaced shocks, each administered to a different preganglionic pathway.

It was found that two types of response were obtained, largely dependent on which combination of preganglionic pathways was selected. With the majority of combinations no summation was obtained when the two preganglionic impulses reached the ganglion at the same time or very shortly after each other. This period extends about 1.5 msec. to each side of the time of simultaneous arrival. With longer intervals summation regularly occurs up to 5 to 15 msec., after which no summation is present. In the second type of summation the relations are the same for longer intervals, but here summation does occur when the two impulses reach the ganglion simultaneously or with intervals shorter than 1 msec. With

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slightly longer intervals there is no summation, but the range of intervals giving this effect is very limited. The second type of summation is characteristic of only one combination, namely that of the two medial giant fibers, whereas it occurs rarely with certain other combinations. These results do not permit themselves to be readily explained by any of the prevalent views on the nature of synaptic transmission.

¹ *J. Neurophysiol.* 10, 23 (1947).

ZADINA, R. (Prague). The study of antagonism on the isolated intestine.

An isolated guinea-pig intestine is a convenient reagent for the study of antagonism, because there are no automatic contractions. In our experiments we have produced contractions with acetylcholine, histamine, or arecoline and we have constructed the concentration-action curve both before and after adding the antagonist. The curves, we have in this way gained, are divided into two groups, according to their shape. The difference is more obvious in the semilogarithmic scale than in the normal.

The first type is characterized (in semilog. scale) in that, concentration-action curves are similar, but with rising doses of antagonist they are displaced to the right. This applies to acetylcholine-atropine, a.-novocaine, histamine-synthetic antihistamines, h.-novocaine, h.-nicotine, h.-atropine, and arecoline-atropine. In the above-quoted cases the antagonist produces the same percentage of inhibition in small as in great doses of histamine or acetylcholine producing one curve.

The second type differs from the first in that in addition to the displacement to the right, at the same time the 100% contraction is lower. The antagonistic poison in small doses of histamine or acetylcholine produces a smaller percentage of inhibition than in great doses. This applies to histamine-harmine, acetylcholine-harmine, and a.-antergan. Similarly as in both first and second types the plot of dose of histamine or acetylcholine injected against the amount antagonized shows a direct proportionality.

ARON, M., et ARON, C. (Strasbourg). **Recherches sur le fonctionnement thyroïdien.**

En 1929, Max Aron¹ et L. Loeb et Bassett² ont montré que la pré-hypophyse sécrète une hormone, la thyro-stimuline (M. Aron) ou thyrotrophine, qui régit l'activité de la thyroïde. M. Aron,³ grâce à des injections d'extrait préhypophysaire à des jeunes cobayes, dont la thyroïde est très peu active, a établi les tests morphologiques du fonctionnement thyroïdien, caractérisés notamment par l'épaississement de l'épithélium vésiculaire et par la vacuolisation de la colloïde (vacuoles de résorption) en fonction du degré d'activité de la glande.

Nous avons utilisé ces tests pour déterminer l'influence directe, sur la thyroïde, de diverses substances, particulièrement de corps iodés, d'extrait thyroïdien, de thiourée, qui, selon une technique nouvelle, ont été introduites dans un des deux lobes thyroïdiens, chez des cobayes adultes. La réaction du parenchyme thyroïdien s'apprécie facilement grâce à la comparaison entre le lobe inoculé et le lobe intact et, dans le lobe inoculé, entre la zone limitrophe du produit introduit et le reste de la glande.

Dans une première série d'expériences, nous avons utilisé ainsi de l'iode métalloïdique, de l'iodure de potassium, de la diiodotyrosine et de la thyroxine. Les quantités de ces substances introduites dans la thyroïde ont varié entre 0.2 mg. et plus d'1 mg. Dans tous les cas, le résultat, après 1 à 3 jours, a été une vive hyperactivité, prédominante au contact immédiat du corps inoculé.⁴

Dans une deuxième série d'expériences, nous avons éprouvé, selon la même méthode, l'effet de l'extrait total de thyroïde, supposé contenir l'hormone thyroïdienne. Dans plusieurs expériences, cet extrait a provoqué une légère, mais nette hypoactivité thyroïdienne dans la zone limitrophe de la substance inoculée. L'irrégularité des résultats obtenus est à rapporter à la faible teneur en hormone de l'extrait, introduit dans la glande à des taux de 200 à 500 gammas seulement. Toutefois les résultats positifs suffisent à attester que l'hormone thyroïdienne *in situ* est capable, à une certaine concentration, d'inhiber le fonctionnement thyroïdien.

Nous avons procédé à diverses expériences-témoins en introduisant dans un lobe thyroïdien des corps banaux, tels que chlorure de sodium, phosphate de calcium et surtout bromure de sodium, afin

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d'établir la spécificité de l'ion iode. Tous ces essais ont été négatifs, aussi bien dans le sens d'une inhibition que dans celui d'une excitation.

Nous concluons que tout se passe comme si les produits intermédiaires du métabolisme de l'hormone thyroïdienne avaient la propriété de stimuler la cellule thyroïdienne, et que son hyperactivité sous l'influence de la thyrotrophine est vraisemblablement en rapport avec la fixation et la formation de ces produits intermédiaires.

L'action inhibitrice de l'hormone thyroïdienne *in situ* suggère qu'un équilibre est institué entre les produits intermédiaires du métabolisme de l'hormone, stimulants de la cellule, et l'hormone même, inhibitrice.

Enfin une dernière série d'expériences a concerné l'introduction de thiourée dans la thyroïde, toujours grâce à la même technique. Il en résulte, autour de la région d'inoculation, des aspects d'hyperactivité analogues à ceux que produisent les corps iodés précités. Nous croyons démontrer ainsi que l'action de la thiourée sur la thyroïde est directe (dans son expression morphologique d'hyperfonctionnement) et non en relation avec un relais préhypophysaire. Nous interprétons les signes d'hyperfonctionnement en question comme dûs à l'accumulation, dans la cellule thyroïdienne, des produits intermédiaires du métabolisme de l'hormone thyroïdienne, dont on admet que la thiourée empêche la synthèse, et dont nous avons montré l'action excitatrice sur la thyroïde.

¹ C. R. Soc. Biol. 102, 682 (1929). ² Proc. Soc. Exp. Biol. and Med. 26, 860 (1929). ³ Rev. fr. d'endocrinol. 8, 472 (1930). C. R. de l'Ass. des anat. 29 (1934).

⁴ Alors qu'il apparaît que la thyroxine, *in situ*, excite le fonctionnement thyroïdien, on sait, depuis les expériences de Courier (C. R. Soc. Biol. 91, 1274 (1924)), de Courier et Aron (C. R. Soc. Biol. 100, 89 (1929)), et de M. Aron (C. R. Soc. Biol. 104, 96 (1930)), qu'en injection sous-cutanée elle l'inhibe. Il apparaît là que la thyroxine injectée acquiert, dans le milieu intérieur, vraisemblablement en entrant en liaison avec des protides, des propriétés différentes de la thyroxine pure, et analogues à celles de l'hormone thyroïdienne, qui, elle aussi, sous forme d'extrait thyroïdien, inhibe la thyroïde quand on l'injecte ou qu'on l'ingère à des cobayes ou autres mammifères.

ARVANITAKI, A., et CHALAZONITIS, N. (Tamaris-sur-Mer (Var), France). Structures électroactives et potentiels d'activité cellulaires.

Il est probable que les potentiels d'activité cellulaires trahissent principalement les variations de l'activité électronique, etc.¹ La question déjà posée sous une forme ou sous une autre^{2, 3} est ici traitée par trois méthodes: On admet que les propriétés des atomes transporteurs (transfert, électroactivité, couleur etc.) sont fonction de leur coordination particulière avec d'autres groupes d'atomes.^{4, 5, 6} Toute modification portant sur cette coordination se répercuterait à la fois sur la vitesse de réaction avec l'électron, et *in vivo* sur la 'synchronisation' du transfert. En fait, la coordination complémentaire *in vivo* de différents réactifs aux métaux lourds intracellulaires modifie l'électrogenèse (axone isolé de *Sepia*). Les anions complexogènes tels que pyruvate, pyrophosphate, fluorure, nitrite etc. initient l'activité oscillatoire autoentretenue dont les caractéristiques (vitesse, fréquence etc.) sont fonction de la nature de l'anion coordonné complémentirement; les cyanure, sulfhydrate, CO, inhibent instantanément toute activité.^{7, 8, 9}

Plus directement, l'absorption spécifique des groupements électroactifs permettrait de les 'observer' *in vivo* par enregistrement simultané des spectrogramme et électrogramme. Ainsi sur le ventricule isolé d'*Helix* l'analyse photométrique du spectrogramme à différents temps durant la diastole (pour éviter phénomènes optiques équivoques revenant à la contraction) révèle au moment où se déclenche l'ample pointe du potentiel d'activité présystolique l'approfondissement au moins des bandes α des cytochromes avec certaines variations moins spécifiques de la transparence de 'fond'. Réciproquement, leur absorption spécifique permettrait une activation photochimique élective des transporteurs *in vivo*. En fait, l'illumination du ventricule isolé d'*Helix* par différents faisceaux monochromatiques à énergie égalisée, choisis dans différentes zones du visible détermine des variations faibles mais significatives sur les vitesse, fréquence, amplitude de l'électrogramme. Ces variations chiffrées esquissent en fonction de la fréquence activatrice un 'spectre' d'activation photochimique dont les maxima coïncident avec les bandes cytochromiques.

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Ces résultats accusent la prépondérance fonctionnelle du système des cytochromes dans l'électrogenèse cellulaire et indiquent la contribution probable d'autres systèmes.

- ¹ Arvanitaki et Chalazonitis, *Arch. Intern. Physiol.* **54**, 423 (1947). ² Gerard, *Cold Spring Harbor Symp.* **4**, 194 (1936). ³ Lund, *J. Exp. Zool.* **51**, 291 (1928). ⁴ Wurmser, *L'Électroactivité dans la chimie des cellules*, Hermann, Paris (1935). ⁵ Barron, *Cold Spring Harbor Symp.* **7**, 154 (1939). ⁶ Keilin et Hartree, *Proc. Roy. Soc. B.* **127**, 167 (1939). ⁷ Arvanitaki et Chalazonitis, *Arch. Intern. Physiol.* **54**, 406 (1927). ⁸ Id. 441. ⁹ Schmitt, *Am. J. Physiol.* **95**, 650 (1930).

BAUMBERGER, J. PERCY (Stanford, Calif.). The oxygen tension of whole blood measured polarographically.

In 1938 the author measured the oxygen tension of dilute blood polarographically in order to determine the oxygen dissociation curve of oxyhemoglobin. In 1942 *Berggren* applied the polarographic method to the study of oxygen tension of blood in cases having non-ventilated parts of the lungs. He was unable to use whole blood because of interference of oxyhemoglobin with the determination but finally used plasma successfully.

There are advantages, however, in determining the oxygen tension of whole blood and this was accomplished as described below. If blood and Ringer's solution are equilibrated with the same gas in separate bulbs of a tonometer by rotation for a half-hour, the two fluids come to identical oxygen tensions. This blood gives a diffusion current on the dropping mercury electrode far greater than the mammalian Ringer's (plus caffeine as maxima suppressant) although both fluids have identical oxygen tensions. This difference is particularly evident at an applied voltage of -0.5 V. (referred to the saturated calomel half-cell as zero) and less so at -1.5 V. When the oxygen tension of the equilibrating gas is low enough to allow the hemoglobin to be partially reduced, these differences are increased. Haemolysis further increases these differences.

The addition of cyanide in low concentrations brings the diffusion current at -0.5 V. of blood and Ringer's into agreement and cyanide in higher concentration accomplishes the same thing at -1.5 V. The diffusion current in blood at -0.5 V. is due in part to the reduction of oxygen to hydrogen peroxide and in part to the catalytic decomposition by methemoglobin of the hydrogen peroxide

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formed. This catalase activity is eliminated by cyanide. The diffusion current at -1.5 V. is due in part to the reduction of oxygen to hydroxyl ion and in part to the reduction of ferrous ion to metallic iron. The latter is eliminated by the mass action conversion of ferrous ion to ferrocyanide which is not reducible. Therefore addition of cyanide leaves the diffusion currents at -0.5 and 1.5 V. linear functions of oxygen tensions both in Ringer's and in blood.

The addition of cyanide therefore makes it possible to determine the oxygen tension of blood polarographically. Samples of blood drawn with the usual precautions against gaseous interchange, coagulation, and aging, when cyanide is added, will show oxygen tensions corresponding to those of the circulating blood.

BENOIT, PAUL H. (Asnières (Seine) France). Electric excitation of muscle by currents of very short duration.

The threshold quantity of electricity becomes constant if it is discharged through the nerve within a very short time: this was formerly claimed by *Cremer* and his school, both on theoretical and experimental grounds. Unfortunately the evidence put forward was far from being conclusive and the matter remained uncertain until it was settled once for all by the work of *Ph. Fabre*.¹ In recent years, *Fabre's* results have been fully confirmed and extended to different types of nerves by numerous authors. Moreover, a constant quantity law for extremely short discharge-times is predicted by *Monnier's* and *Hill's* theories: according to the latter, it forms 'a crucial test for any excitation formula'.

Is this law still valid in the case of muscle stimulation? In *Katz's* pre-war review,² the α -excitability of muscle is quoted as an 'important exception' from the general rule. In fact *Rushion's*³ data for rectangular pulses show clearly that a constant quantity plateau is far from being reached even for currents lasting $0.2-0.5$ msec., i.e. about one-hundredth of the α excitation-time of the frog's sartorius. On the other hand, nerve data (*Fabre*) indicate that this plateau is reached for 0.01 msec., i.e. only one-thirtieth of the frog's sciatic chronaxie.

We tried to get muscle data for shorter times. Condenser discharges and large fluid electrodes were used: the stimulating device

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was the same as *Fabre's*. The experiments were performed on denervated muscle, in order to avoid nerve stimulation. Our results indicate that the threshold quantity becomes constant for discharge-times of the same order of magnitude as in nerve excitation. For instance, in eight experiments on frog's sartorius, the mean value for the discharge-time where the quantity curve leaves its plateau was found to be about 0.014 msec. (against 0.010 in four experiments on sciatic nerve). In the same experiments, the mean values for the muscle α -excitation-time and the nerve chronaxie were respectively 26 and 0.3 msec.

So nerve and muscle show almost identical time-constants when tested by sufficiently short currents, despite of experimental conditions leading to heterochronism. This result strongly supports the view according to which the processes underlying the α -excitability for brief pulses are different from those for long lasting currents. Summation experiments⁴ had previously led to a similar conclusion which is consistent with the evidence provided by the study of delayed repetitive responses in nerve and muscle.

¹ Fabre, Ph., *C. R. Acad. Soc.*, Paris, 190, 449 (1930). Fabre, Ph., and Swyngedauw, J., *C. R. Soc. Biol.*, Paris, 113, 765 (1933). Fabre, Ph., Quesnoy, P., and Berteaux, J., *C. R. Soc. Biol.*, Paris, 115, 1431, and 116, 179 (1934).

² Katz, B., *Electric Excitation of Nerve*, Oxford University Press (1939).

³ Rushton, W. A. H., *J. Physiol.* 72, 265, &c. (1931). ⁴ Benoit, P. H., and Benoit, M., *C. R. Soc. Biol.*, Paris, 131, 1244 (1939).

BEST, C. H., LUCAS, C. C., PATTERSON, JEAN M., and RIDOUT, JESSIE H. (Toronto). Factors involved in the determination of the relative potencies of the lipotropic agents.

The proper background against which to estimate the relative potencies of the lipotropic agents, choline, betaine, and methionine, is obviously a diet which contains none of these factors. The situation is complicated by the fact that if we completely eliminate methionine, which is one of the sources of choline in the body, the diet is not adequate for the growth of young animals. Furthermore, when large groups of rats are used, it is not feasible to provide a diet completely free of methionine since the only way to do this is to feed rations in which the nitrogen is supplied as purified amino acids. We have, therefore, adopted a standard diet very low in methionine, but

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believed to be adequate in other respects, and have determined the minimum dose of choline which gives a maximum effect under a variety of conditions. The addition of cholesterol to the diet increases the choline requirement while the effect of fat is much less definite.

Since choline is the effective agent when betaine and methionine are fed, in so far as their lipotropic action is concerned, and since choline is the most potent of the lipotropic agents, the activities of betaine and methionine have been expressed in terms of choline. The amount of choline which is equivalent to the minimal amount of methionine or betaine which gives a maximal effect has been estimated under several dietary conditions. The demand for methionine is, as others have previously shown, increased during active growth. Choline and cystine can apparently replace a part of the effect of methionine on growth, i.e. the minimal amount of methionine required for normal growth appears to be less than previous estimates, if choline and cystine are also provided.

The toxicity of small supplements of cystine when certain diets are used is due, as *Griffith* originally showed, to an intensification of the demand for choline. These toxic signs produced by cystine, which are typical of choline deficiency, are not observed when diets containing adequate amounts of choline or its precursors are present.

The relative potencies of choline and methionine may be estimated not only on prevention of deposition of fat in the liver but also by their action in protecting the kidney of the young rat or in the alleviation of cirrhosis produced in older animals by various means. The results of some of these determinations will be presented and discussed.

BINET, LÉON, et STRUMZA, M.-V. (Paris). L'Apnée par hyperthermie ; variations avec l'inhalation d'oxygène.

Nous nous sommes attachés à démontrer expérimentalement qu'un facteur anoxique secondaire à l'hyperthermie intervient avec celle-ci, dans le déterminisme de l'apnée.

L'hyperthermie est réalisée en soumettant un chien chloralosé aux effets des ondes courtes, les électrodes étant placées de part et d'autre de la région thoraco-abdominale au niveau du foie. L'élévation

continue de la température centrale entraîne initialement une excitation de la respiration, suivie lorsque la température dépasse 43° C d'une inhibition progressive. Au-dessus de 44° la ventilation pulmonaire baisse rapidement et les besoins en oxygène de l'organisme, considérablement accrus par l'hyperthermie, ne sont plus satisfaits. L'animal se cyanose et l'apnée survient entre 44° 5 et 45° 5, moyenne 44° 9.

La respiration d'oxygène pur assure une hématoxémie satisfaisante malgré une réduction marquée de la ventilation pulmonaire, et dans ces conditions, l'apnée ne s'observe plus qu'avec une température de 46° à 47°, moyenne 46° 2.

Si l'animal inhale un mélange gazeux appauvri en oxygène mais n'entraînant pas par lui-même l'apnée avec une température normale, la mort s'observe dès le fléchissement de la ventilation pulmonaire. Avec une tension partielle d'oxygène de 60 mm. Hg. l'apnée est notée entre 43° 3 et 43° 8.

La sensibilité périphérique intervient dans l'établissement de l'hyperpnée thermique mais ne joue pas de rôle dans l'inhibition ultérieure. C'est l'effet direct de l'hyperthermie sur les centres nerveux qui compte: des animaux à température rectale à 48° et 49° par exposition du bassin aux ondes courtes continuent à respirer jusqu'au fléchissement cardiaque, si le bulbe est réfrigéré. Contre les électrodes, les tissus peuvent atteindre pendant des heures des températures de 55°-60°-70° sans entraîner l'apnée tant que les centres nerveux ne sont pas surchauffés. Enfin, une élévation de la température du bulbe, les électrodes étant mises au cou, entraîne l'apnée avec une température rectale relativement basse, 42° et même 40°.

Lorsque les centres respiratoires commencent à être inhibés par l'hyperthermie, ils deviennent insensibles à divers excitants: éphédrine, anoxémie. Par contre, ils sont très sensibles aux dépresseurs: morphine, barbiturique, chloralose.

Ainsi, la mort par hyperthermie observée avec une température inférieure à 45° est d'origine anoxique, mais l'inhibition respiratoire liée à l'élévation de la température des centres respiratoires paraît irréversible.

BINET, L., et WELLERS, G. (Paris). L'Importance des liaisons -SS- pour la toxicité du venin de cobra.

Les travaux d'une série de chercheurs et principalement ceux de *F. Meechel* et ses collaborateurs et de *K. H. Slotta* et *H. L. Fraenkel-Conrat*, ont précisé de multiples détails concernant l'importance des liaisons du soufre pour l'activité des venins de serpents. Cependant la nature de ces liaisons reste discutée. Certaines de nos observations contribuent à apporter de la clarté à ce problème.

Si l'on soumet le venin de cobra à l'action du CNK on constate trois phénomènes liés entre eux: 1°) l'atténuation de la toxicité, 2°) l'apparition d'un pouvoir réducteur et 3°) l'apparition d'une réaction positive au nitroprussiate. L'intensité de ces trois phénomènes dépend de la concentration du CNK et de la durée de son action. Cependant les trois phénomènes se manifestent d'une façon discontinue au fur et à mesure que la concentration du CNK croît. Notamment dans des solutions de CNK dont la concentration ne dépasse pas 0.75 % le venin de Cobra perd la moitié de sa toxicité, absorbe environ 1 c.c. d'iode N/500 pour 25 mg. et présente une faible mais nette réaction au nitroprussiate. Dans les solutions de CNK dont les concentrations sont comprises entre 1 et 1.5 % le venin perd environ 90 % de sa toxicité, absorbe environ 2 c.c. d'iode N/500 pour 25 mg., et manifeste une forte réaction au nitroprussiate. Dans des solutions de CNK dont les concentrations sont supérieures à 2.5 % (les essais étaient effectués avec des concentrations allant de 2.5 à 17 %), le venin perd plus de 98 % de sa toxicité, absorbe environ 3 c.c. d'iode N/500 pour 25 mg., et donne une très forte réaction au nitroprussiate. L'ensemble de ces phénomènes permet de conclure que la neurotoxine du venin de Cobra possède trois groupes de liaisons -SS- différemment accessibles à l'action du cyanure: le premier facilement réductible par CNK, le second plus difficile à atteindre et le troisième qui n'est atteint que par de fortes concentrations de CNK. La présence des liaisons -SS- est donc indispensable pour que le venin de cobra puisse manifester ses propriétés physiologiques. Leur réduction par CNK en groupement -SH conduit à la perte de la toxicité.

BRAUN-MENENDEZ, EDUARDO (Buenos Aires). The mechanism of renal hypertension.

Hypertension due to renal ischemia is due to a generalized vasoconstriction; the nervous system does not play a primary part in this type of hypertension. The generalized vasoconstriction is thus of humoral origin.

A pressor and vasoconstrictor substance has been found in the renal venous blood of animals made hypertensive by partial constriction of the renal artery and of animals in which acute partial or total ischemia of the kidneys is produced. The substance responsible for this action is renin. *Renin* is an enzyme which is secreted by the kidney into the blood and has no vascular action of its own. Its pressor and vasoconstrictor activity depends upon *hypertensin* which is a substance formed by the interaction of renin with *hypertensinogen*, the latter being a globulin present in blood-plasma. The polypeptide *hypertensin* is, in turn, destroyed by *hypertensinase*, an enzyme or group of enzymes, present in the blood and in extracts of most organs.

Human hypertension is in some cases undoubtedly of renal origin. In the hypertension produced in man by unilateral renal lesions removal of the affected kidney abolishes the hypertension.

Renin has been detected in the arterial blood of dogs during the first days following renal ischemia and of a few human beings during the acute phase of hypertension (acute glomerulonephritis, toxemia of pregnancy). But in animals with chronic hypertension with or without renal insufficiency as well as in patients with essential hypertension the results have been negative. This difference between acute and chronic hypertension may be due to a difference in concentration of renin. Using more sensitive methods renin was found in men, dogs, and rats with chronic hypertension and also in perfectly normal cases.

These and other experimental data which will be reported are in favour of the view that the renin-hypertensin system is not the sole cause of renal hypertension and that other chemical mediators may play an important part in the causation of chronic hypertension of renal origin.

CAMPBELL, R. M., and KOSTERLITZ, H. W. (Aberdeen).
Relationship between losses in labile liver cytoplasm and urinary nitrogen excretion.

When rats are transferred from an adequate stock diet to a protein-free diet, female rats lose 26% and male rats 36% of their liver cytoplasm in 5 days (Kosterlitz, 1944, 1947; Campbell and Kosterlitz, 1946). It has also been observed in many species that under similar conditions the excretion of nitrogen gradually falls until a relatively constant value is reached on the fifth or sixth day (Voit, 1866; cf. Kosterlitz and Campbell, 1945-6). The excretion of this 'extra nitrogen' during the first few days of a protein-free diet appears to be closely correlated with the loss of labile cytoplasm from the liver.

Female rats which were transferred from the stock diet to a protein-free diet containing 60% potato starch and 25% sucrose excreted 46.8 mg. 'extra nitrogen' /100 gm. body-weight in 4 days (mean of 4 rats) while the loss of protein (+ nucleic acid) nitrogen from the liver amounted to 26.8 mg./100 gm. body-weight. Female rats transferred to a protein-free diet containing 85% sucrose excreted 47.3 mg. 'extra nitrogen' /100 gm. body-weight in 5 days (mean of 4 rats) while 26.8 mg. protein nitrogen /100 gm. body-weight were lost from the liver (mean of 5 rats). In these two experiments 57% of the 'extra nitrogen' was accounted for by the loss of labile liver cytoplasm. Male rats transferred to a protein-free diet containing 60% potato starch and 25% sucrose excreted 40.7 mg. 'extra nitrogen' /100 gm. body-weight in 5 days, of which 39.5 mg./100 gm. body-weight or 97% were accounted for by the loss of labile liver cytoplasm (mean of 4 rats).

Voit (1866), Rubner (1911), and others assumed that the 'extra nitrogen' excreted during the first few days of a protein-free diet was unorganized 'circulating' or 'storage' protein which acted as a reserve pool for protein metabolism. The data of this communication, however, indicate that at least 60% and probably more of the 'extra nitrogen' is derived from liver proteins. Recent observations (Kosterlitz, 1944, 1947; Campbell and Kosterlitz, 1947) have shown that not only proteins but also corresponding amounts of phospholipids and ribonucleic acid are lost from the liver. It would appear then

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that the greater part of the 'extra nitrogen' in the urine is derived from a breakdown of liver cytoplasm.

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Kosterlitz, H. W., and Campbell, R. M., *Nutr. Abstr. Rev.* **15**, 1 (1945-6).
Rubner, M., *Arch. Anat. Physiol.*, Lpz., *Physiol. Abt.* 61 and 67 (1911).
Voit, C., *Ztschr. Biol.* **2**, 307 (1866).

CARIDROIT, F. (Paris). **Du rôle de l'hormone thyroïdienne dans la réceptivité de la crête à l'hormone mâle.**

La croissance de la crête du chapon sous l'influence des hormones mâles est suffisamment constante pour qu'elle ait été prise comme test dans la définition de l'unité internationale. Pourtant les conditions externes (température, lumière) peuvent la modifier. Elles agissent soit directement sur le tissu même de la crête, soit indirectement par l'intermédiaire de facteurs internes qui changent la réceptivité de la crête. Parmi ces derniers, l'hormone thyroïdienne paraît le plus important d'après les expériences que nous rapportons.

1° La thyroxine diminue le seuil de réponse de la crête du chapon. Deux groupes de chapons reçoivent une injection unique de 25 γ de propionate de testostérone mais l'un d'eux a, en plus, 5 injections de 1 mg. de thyroxine. Seuls les chapons de ce groupe ont une croissance de la crête.

2° Des chapons conditionnés stables à 15 γ et à 30 γ de propionate de testostérone reçoivent de la thyroxine en injections intramusculaires ou par la bouche. Immédiatement, leur crête se remet à croître.

3° La crête d'un chapon thyroïdectomisé ne change pas après l'injection unique de 100 γ de propionate de testostérone mais si, en même temps, on administre quelques injections de thyroxine (5 fois 1 mg.), elle s'allonge de 4 mm.

4° Une injection unique de 400 γ de propionate de testostérone fait grandir la crête d'un chapon jusqu'à un maximum atteint en 5 jours; la régression commence ensuite et se continue. Mais si, au cours de la régression, on donne 1 mg. de thyroxine par jour, la crête se stabilise pendant 9 jours avant que la diminution recommence. Il est normal qu'une régression qui suit une castration ne soit pas interrompue par la thyroxine.

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5° Quelle que soit la nature de l'hormone androgène l'action favorisante de la thyroxine reste toujours manifeste. Nous avons fait les expériences avec une injection unique de 25 γ d'acétate de testostérone (avec et sans thyroxine), avec 5 fois 100 γ d'androsterone (avec et sans thyroxine), avec des extraits urinaires androgènes (avec et sans thyroxine), injections 5 jours de suite.

6° Un extrait thyroïdien est plus actif que la thyroxine à teneur en iode thyroïdien égale.

7° Le dinitriphénol, qui augmente le métabolisme, n'exerce aucune action favorisante.

8° La dose optima journalière de thyroxine est comprise entre 1/2 mg. et 1 mg. Avec 1/4 mg., nous n'avons généralement pas de résultats et avec 2 mg. l'action n'est pas plus forte qu'avec 1 mg.

Conclusion: L'hormone thyroïdienne favorise d'une façon très nette l'action des hormones androgènes sur la crête du chapon. On sait que la thyroïde des oiseaux maintenus à l'obscurité a sa sécrétion qui augmente, d'où l'explication de l'augmentation de la crête des coqs mis à l'obscurité.

DOWNMAN, C. B. B., and VASS, C. C. N. (London). **Sensitivity of the intestine to applied stimuli.**

Severe trauma to the intestine, such as crushing or cutting, does not cause pain in man. Distension and spasm do cause pain. *Hurst* (1911) suggested that the latter stimuli affected nerve endings which respond only to tension within the gut wall. *Meyer* (1919) found that these stimuli did not cause pain-reactions in cats when the mesentery was protected from stretch. One could argue that the intestine is insensitive, any pain accompanying intestinal disorder arising at second-hand from the sensitive mesentery.

Lewis and Kellgren (1939) were unable to produce reflex contraction of belly muscle by pinching the intestine of spinal cats. Pinching the pancreas did cause these visceromotor responses. In both instances there was rise of arterial pressure. This suggested that the intestine does lack a system of afferent fibres affecting spinal anterior horn cells. *Downman and McSwiney* (1946) recorded visceromotor reflexes on stimulating both intestine and pancreas, using decerebrated cats with the spinal cord sectioned at T. 1. Visceromotor

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reflexes from the intestine were more fragile than those from the pancreas, and visceromotor reflexes were lost before alteration of vascular response. These changes occurred with repeated stimulation of the preparation, or with the trauma of sham splanchnicectomy. Continuing these studies it has been found that the intestine and mesentery are sensitive to such agents as cutting, crushing, pinching, temperature above 46° C., 10% sodium chloride, 1.3% potassium chloride, N/10 hydrochloric acid. Application to the outer surface of the intestine elicits pupil dilatation in chloralosed cats, and rise of arterial pressure with leg movements in decerebrated spinal cats. The stimuli were effective when they were applied to the intestine and were prevented from spreading on to, or indirectly affecting, the intestinal mesentery. It is concluded that the sensitivity of the intestine is independent of mesenteric sensory endings. Scratching the surface and pinching the wall of the intestine after removing the mucosa caused reflex responses. It is suggested that the nervous structures involved lie in or close to the serosa. No responses were obtained on pinching the mucosa, heating it to 60° C., nor applying irritants such as mustard.

The relation between reflexogenic impulses and pain impulses is a matter for speculation.

Downman, C. B. B., and McSwiney, B. A., *J. Physiol.* 105, 80 (1946). Hurst, A. F., *The Sensibility of the Alimentary Canal*. London: Oxford Medical Publications (1911). Lewis, T., and Kellgren, J. H., *Clin. Sci.* 4, 47 (1939). Meyer, A. W., *Dtsch. Zeit. Chirurg.* 151, 153 (1919).

ELKES, J., and FINEAN, J. B. (Birmingham). Observations on the structure of certain lipoproteins.

Reversible adsorption of proteins at charged oil/water interfaces has been demonstrated in previous experiments.¹ The formation of complexes between detergents and proteins in the absence of an interface has also been observed, and this has confirmed certain findings of other workers.² The haemoglobin/sodium cetyl sulphate system offered a convenient model for the study of lipoproteins. As in an interfacial system, association here was found to be pH conditioned and reversible. A zoning phenomenon was also observed, both insoluble and soluble complexes being formed according to the molecular ratio of detergent to protein.

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X-ray diffraction studies were carried out on frog sciatic nerve, and significant changes, both in long and short spacings, were obtained by low temperature treatment with alcohol, ether, chloroform, acetone, dioxan and pyridine. The relation of these results to the work of others^{3, 4} will be discussed.

¹ Elkes, J., Frazer, A. C., Schulman, J. H., and Stewart, H. C., *Proc. Roy. Soc. A*, **184**, 102 (1945). ² Putnam, F. W., and Neurath, H., *J. Amer. Chem. Soc.* **66**, 692 (1944).

³ Boehm, G., *Kolloid Ztschr.* **62**, 22 (1933).

⁴ Schmitt, F. O., Bear, R. S., and Clark, G. L., *Radiology*, **25**, 131 (1935).

EMMELIN, N. (Lund), and FELDBERG, W. (Cambridge). **The mechanism of the nettle sting reaction.**

The fluid of the hairs of the nettle (*Urtica urens*) contains at least three pharmacologically active substances: histamine, acetylcholine, and an unidentified smooth muscle-contracting substance. The identification of histamine and acetylcholine is based on pharmacological reactions and on some physico-chemical properties. Histamine is present in the hair fluid in a concentration of about 1 in 500 to 1 in 1,000 and is responsible for the triple response and the itching sensation produced by the sting of the nettle hair on the human skin. Acetylcholine is present in the hair fluid in a concentration of about 1 in 100 or stronger. The absence of cholinesterase in this fluid made it easy to determine the acetylcholine content of individual hairs. The acetylcholine is in part responsible for producing the burning sensation of the sting of the nettle hair. It was found that acetylcholine 1 in 100 pricked into the skin caused no definite sensations but produced burning pain when introduced together with histamine. No function could yet be attributed to the unidentified smooth muscle-contracting substance present in the fluid of the nettle hair.

Histamine and acetylcholine occur also in the leaf tissue of the nettle plant, but in much weaker concentrations than in the hairs. The possibility exists that these substances are formed in the leaves, transported to the hairs, and there concentrated.

ENGBÆK, LISE (Copenhagen). Effect of magnesium on the neuromuscular junction.

The localization of the peripheral action of magnesium on striated muscle is still open to discussion. Recently the problem has got more actual interest as magnesium distinctly abolishes the interaction between myosine and adenosine triphosphate. Greville and Lehmann (1943) have interpreted this observation as a muscular localization of the peripheral magnesium effect, while most of the earlier investigations are interpreted as a motor endplate effect of magnesium. Direct application of minute amounts of acetylcholine to the motor endplate causes a rapid contraction, thereafter all subsequent doses of acetylcholine are ineffective, while the reaction to potassium and electric stimulation is retained (Buchthal and Lindhard, 1942). These findings were interpreted by assuming two physiological boundary faces in the motor endplate: The first between the motor nerve endings and the sole of the endplate, the second between endplate and muscle fibre. The first boundary face is blocked by acetylcholine, which has no effect on the other since potassium and electric stimulation are still effective. The quick contraction caused by acetylcholine is abolished by curarine, which rapidly blocks the first boundary face while the second is influenced more slowly. The purpose of this work has been to investigate the magnesium effect on the single motor endplate, especially how far magnesium affects the different boundary faces.

The experiments are performed on a single layer of lizard muscle fibres, and variations in excitability of the single endplate compared with those of the corresponding nerve.

Magnesium (4.1–8.2 mM/l) blocks stimulation through the nerve, while irritability of the endplate remains unchanged. Higher concentrations of magnesium (123–144 mM/l) increase the threshold for endplate stimulation. This is interpreted as being due to a high sensibility of the first boundary face to magnesium. The contractions caused by acetylcholine are likewise abolished by magnesium (21–62 mM/l) and the higher the acetylcholine concentration the higher is the concentration of magnesium needed to produce a blockade, so that magnesium like curarine abolishes the contractions caused by direct application of acetylcholine to the motor endplate.

FALCONER, J. S. (Newcastle-upon-Tyne), and TAYLOR, D. B. (London). A general quantitative method for the purification of proteins with specific, accurately measurable, properties.

There are three closely related types of solubility test in use in protein chemistry at present. Using the terminology suggested earlier (Falconer and Taylor, 1946) these are:

(1) The 'Constant Solvent' test (Sorensen and Hoyrup, 1917), (Northrop and Kunitz, 1930).

In this test an analysis is made of the solubility of increasing quantities of a mixture of proteins in a solvent of constant composition at constant pH and temperature. The composition of the solution tested and the solubility of each protein in the solvent used can be obtained by a method of analysis described by Northrop and Kunitz (1938).

(2) The 'Variable Solvent' test.

The alternative method of experimental analysis where the total protein, temperature, and pH were constant and the precipitating salt concentration increased, was also carried out by Sorensen and Hoyrup (1917). Moreover, they showed that the behaviour of the proteins in this type of test was also governed by the phase rule. More detailed use of this experimental approach has been made by many workers, Butler, Blatt, and Southgate (1935), Roche, Dorier, and Samuel (1936), and Jameson and Roberts (1937).

That these tests are related and that the 'Constant Solvent' test is a special case of the 'Variable Solvent' test can be easily demonstrated. This relationship between the tests is important in deciding which test to use. The difference in sensitivity and resolving power between the two tests and the different types of information they provide must also be taken into account.

(3) The 'Specific Property' test (Falconer and Taylor, 1946.)

In this test, the 'Variable Solvent' test is used and the precipitation of both the total protein present and the activity (or any other accurately measurable property) of the protein to be purified is measured. By plotting the precipitation of the activity of the protein under investigation against the precipitation of the total protein it is possible to obtain an analysable picture of the overlap of the

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precipitation ranges of the protein to be purified and the impurities. In this way the overlap can be examined and the results used to deduce a method of purification. The test can also be used as a criterion of purity of the final product.

It seems possible in certain cases by the use of the specific property test to deduce the optimal conditions necessary for purification of a given protein. The effect of concentration or dilution of the solution before fractionation can also be predicted.

Two methods of analysis of 'Specific Property' tests are available, a graphical method and an algebraic. These two methods give results which differ in many ways, but the data they provide are complementary. From this information it seems possible to build up a general rational method of protein purification in those cases where the protein has a specific accurately measurable property.

Butler, A. M., Blatt, H., and Southgate, H., *J. Biol. Chem.* 109, 755 (1935). Falconer, J. S., and Taylor, D. B., *Biochem. J.* 40, 835 (1946). Jameson, E., and Roberts, D. B., *J. gen. Physiol.* 20, 475 (1937). Northrop, J. H., and Kunitz, M., *J. gen. Physiol.* 13, 781 (1930). Northrop, J. H., and Kunitz, M., *Col Spring Harbour Symposia*, Vol. 6 (1938). Roche, A., Dorier, M., and Samuel, L., *C. R. Soc. Biol.*, Paris, 122, 231 (1936). Sorensen, S. P. L., and Hoyrup, M., *C. R. Lab. Carlsberg*, 12, 213 (1917).

GERNANDT, B., and ZOTTERMAN, Y. (Stockholm). The effect of respiratory changes upon the spontaneous injury discharge of afferent mammalian and human nerve-fibres.

Injury potentials set up in the afferent fibres of the splanchnic nerve of the cat have been shown to respond in a regular manner to changes in the carbon-dioxide-tension of the blood. Artificial over-ventilation with air as well as the increased ventilation ensuing from breathing gas mixtures low in oxygen produce a very marked increase of the injury potentials, while a rise in the carbon-dioxide-tension of the blood inhibits the discharge.

In full accordance with the above phenomena it was found that the pricking paresthesias following upon the release of the blood-stream to the arm after a previous period of asphyxiation can be modulated in a corresponding way by changing the carbon-dioxide-tension of the subject; hypocapnia increasing them and hypercapnia causing a reduction or abolition of the sensations experienced.

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These findings seem compatible with the view that the variations in the excitability of the mammalian nerve-fibres are produced by changes in the amount of ionized calcium in the tissues.

GREENWALD, ISIDOR (New York). Is endemic goiter due to a lack of iodine?

The 'iodine-lack' hypothesis has been submitted to a critical examination' with the following results:

1. The proponents of the view that there is a deficiency in the iodine intake in goitrous regions have not properly controlled their methods. Many workers did not find the postulated differences in iodine supply. There is one report that different varieties of the same vegetables, grown upon the same soil, at the same time, showed greater variations in their iodine contents than were ever claimed to exist between foods produced in goitrous and non-goitrous areas.

2. Determinations of the iodine content of thyroids, human, sheep, and dog, have, in all published instances, shown that large thyroids, including unquestioned goiters, contained more iodine than did small ones. Therefore, a lack of iodine cannot be considered to have been the cause of the enlargement.

3. Persons with simple goiter do not have a low metabolic rate.

4. Goiters have been produced in rats upon certain iodine-poor diets, but the addition of such small quantities of iodine as are found in ordinary diets has not prevented, nor lessened, the enlargement of the thyroids. Glands of normal size and microscopical appearance have been obtained in rats upon such diets, only by the use of larger amounts of iodine and the accumulation of abnormally high concentrations and amounts in the thyroids.

5. The prophylactic administration of iodine to humans has not reduced the incidence of new goiters to zero. In some places there has been no effect at all, or even an increase in the incidence. Such beneficial effects as have been observed appear to have been due, not to the making good of a deficiency, but to a pharmacodynamic action of iodide.

6. Examination of the records of early explorers, missionaries, and travellers, as well as of English medical and lay literature, shows that goiter was not present in the Americas or in New Zealand

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before the coming of white men and not in England until the eighteenth century. Its history in many regions, notably England and the prairie provinces of Canada, is that of a newly introduced epidemic disease, which spread rapidly from its original focus but became less virulent and, in many cases, disappeared; only to occur again, in one instance, fifty years later.²

¹ Greenwald, I., *J. of Clin. Endocrinology*, 6, 708-41 (1946). ² Greenwald, I., *Bull. of the Hist. of Med.* 17, 229-65 (1945).

GUTTMAN, RITA (Brooklyn, N.Y.). Resistance characteristics of rectifier element in single nerve-fibers.

In 1941 it was shown that the nerve-fiber membrane acts as an electrical rectifier, permitting current to flow more easily outward than inward. The rectifying property was found to decrease reversibly on narcotization or treatment with K and to disappear on death, at which time the membrane acts as an ohmic resistance, permitting current to flow equally easily in both directions. It was felt that it would be interesting to investigate further the resistance characteristics of the rectification curve and to discover, if possible, whether the anodal or cathodal portion or both were affected on loss of rectification.

Experiments were done on the single fiber of *Loligo pealii*, the squid. One end of the fiber was dipped into isosmotic KCl, which served to kill that end and remove all of its rectifying properties. The other end was placed in sea water or experimental solution. The interelectrode stretch was in oil. Resistance offered to an E.M.F. of varying magnitude sent into the fiber first in one direction and then in the other was measured by means of a direct current Wheatstone bridge, and the calculated currents were plotted against applied voltages. Anodal currents and voltages were termed positive and cathodal negative.

The rectification curve thus obtained for a normal nerve-fiber resembles that of a Cu-CuO rectifier. Plotting voltage against current, the experimental curve deviates more from the straight line which would represent an ohmic resistance in the first quadrant, i.e. where current and voltage are positive (the anodal portion of the curve) than in the third quadrant, i.e. where current and voltage are

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negative (the cathodal portion of the curve). As higher voltages are approached voltage increases more rapidly than current in the first quadrant, less rapidly in the third.

On narcotization, treatment with K or death, the anodal portion of the curve changes more than the cathodal as a straight line (representing an ohmic resistance) is approached.

Excitability and resting potentials were measured also. It was found that as time elapses excitability is lost first. Then the resting potential and rectification concurrently disappear. The resting potential and rectification drop at approximately the same rate.

HODES, ROBERT (Philadelphia, Pa.). Conduction velocity of the skeleto-motor nerve-fibers supplying paretic muscles.

The present experiments were undertaken to investigate systematically some observations we made during earlier electromyographic studies, which suggested that a relationship exists between the degree of motor loss in poliomyelitis and conduction velocity of the somatic efferent innervation.

Muscle power was graded by the examining physio-therapist according to the classification of *Lovett*. The electrical studies consisted of the percutaneous application of single supramaximal shocks to the motor nerve and the recording of the muscle action potential thus produced. The potentials, led from small surface electrodes over the activated muscle or muscle group, were amplified by a three-stage condenser-coupled differential amplifier and were photographed from a cathode-ray oscillograph tube on continuously-moving bromide paper. Conduction velocity was measured by stimulating the nerve at two different sites, measuring the latencies of the muscular responses evoked by each shock, and dividing the latency difference by the distance between the points of stimulation.

Action potentials obtained from some 300 paretic muscles of poliomyelitis patients were expressed as per cent. of the voltage of corresponding normal muscles and compared with muscle strength estimated by the clinical test. Such data showed that the size of the action potential indicated the severity of the muscular weakness.

The maximal conduction velocity of the nerve to a paretic muscle was plotted against the maximal voltage of that muscle in over 50

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cases. It was evident from these results that if a given muscle of one patient were stronger than the corresponding muscle of another patient, then the nerves supplying the former would conduct more rapidly than would those innervating the latter.

Two explanations are possible for the close correspondence between the rate of conduction of the residual nervous supply and the degree of muscular damage: (1) An unknown factor (mechanical, metabolic, &c.), elaborated as a result of the disease process, depresses the excitability and slows the rate of conduction of skeleto-motor fibers. (2) The virus or some of its effects (mechanical, metabolic, &c.) has a selective affinity for somatic motoneurons having axons of large diameter.

We have made no choice between the alternative interpretations of our results as yet, but several presently available lines of evidence appear to favor the latter mechanism. Our preliminary histological observations of anterior horn cells of infected monkeys also suggest a neural and muscular involvement dependent on axonal size. Possible causes of the postulated selective destruction will be investigated later.

HOLMES, P. E. B., JENDEN, D. J., and TAYLOR, D. B. (London).

The relationship between structure and action in curarimimetic drugs and the bearing of this on the mechanism of action of acetylcholine.

Classical theory assigned, to the ammonium ion, the structure ($^+\text{NH}_4$) in which the unit positive charge is localised to the central nitrogen atom. That this structure is only a crude approximation has been demonstrated by *Pauling* (1944) who estimates that the charge-distributing effect of ionic covalent resonance in the N-H bonds in the ion reduces the resultant charge on the central N atom to about one-fifth that postulated by classical theory.

In any ion such as $[\text{R}_4\text{N}]^+$ the charge-distributing effect of resonance will depend on the relative electronegativity of the group R and the atom N.

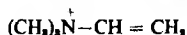
A consideration of the dissociation constants of simple carboxylic acids and of primary, secondary and tertiary amines shows that the ethyl group when compared with the methyl and propyl groups

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behaves as if it had an anomalously low electron-attracting power. We conclude from this that in the tetraethyl ammonium ion the charge-distributing effect is greater than that in the tetramethyl or tetrapropyl ammonium ions. That the curarimimetic activity of tetraethyl ammonium iodide is also anomalous has been known for some time (Ing, 1936).

It appears therefore that for an onium ion to have curarimimetic activity the charge density on the central nitrogen atom must be maintained above a threshold level. A consideration of bond dipole moments in sulphonium, phosphonium, and arsonium ions confirms this.

It has been possible to explain some anomalies in the behaviour of quaternary derivatives of quinoline on the basis of this theory (Holmes, Jenden, and Taylor, 1947). In the case of neurine



the mobility of the electrons in the double bond towards the positive charge can be correlated with its lack curarimimetic activity.

Hunt and Renshaw (1929) demonstrated that if the three methyl groups attached to the nitrogen atom in acetylcholine were replaced by ethyl groups, the molecule lost its activity. It seems that if the positive charge density on the nitrogen atom of acetylcholine falls too low that the molecule becomes inactive.

Holmes, P. E. B., Jenden, D. J., and Taylor, D. B., *Nature*, Lond., 159, 86 (1947). Ing, H. R., *Physiol. Rev.* 16, 527 (1936). Pauling, L., *The Nature of the Chemical Bond*, 2nd edit. (Cornell University Press, 1944). Hunt, R., and Renshaw, R. R., *J. Pharm. and Exp. Therap.* 37, 309 (1929).

JOURDAN, F. (Lyon). Le cœur en rythme nodal expérimental. (Caractères et évolution observés durant cinq années.)

Il est bien souvent difficile d'affirmer, en clinique humaine, même au vu de l'électrocardiogramme, l'origine nodale du rythme cardiaque. Lewis dès 1914, Ganther et Zahn, Meakins et White, Bormann et Meek et surtout Eyster et Meek se sont cependant efforcés de préciser expérimentalement les caractères de ce rythme. Nous avons eu la chance de conserver en vie depuis 1941 deux animaux, sur lesquels nous avons pratiqué l'excision aseptique du nœud sinusal et nous

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avons ainsi pu recueillir, avec R. Froment, un grand nombre de documents électrocardiographiques.

L'ablation du nœud sinusal entraîne, sur la table d'opération, une soudaine réduction de la fréquence cardiaque. Pendant les 10 premiers jours elle demeure cependant assez rapide, 70 à 80 systoles par minute; le voltage de l'onde P varie constamment, tandis que l'intervalle PR, toujours raccourci, est extrêmement instable, l'onde P pouvant s'accoler au complexe, se composer avec lui ou être négative. L'arythmie respiratoire subsiste.

Du 10^{ème} au 40^{ème} jour ralentissement du rythme, P et PR conservent leur variabilité avec accidents auriculaires parfois en position postérieure. De temps à autre des complexes ayant l'aspect d'échappements ventriculaires à la suite de longues diastoles d'origine vagale, car l'atropine les fait disparaître; il en va de même de quelques 'P bloqués'.

Au 6^{ème} mois, PR, en général raccourci, tend à se stabiliser; irrégularités rythmiques moins fréquentes; onde P tantôt positive, parfois négative, de voltage instable.

Actuellement, plus de cinq ans après l'opération, la fréquence cardiaque s'est fixée autour de 80 systoles par minute, tandis que l'arythmie respiratoire subsiste. P est toujours antérieur, mais polymorphe: tantôt positif tantôt négatif et accentué, tantôt apparemment invisible, mais alors une rapide ondulation diphasique, de très faible amplitude, occupe sa position. Le PR est devenu normal. Le complexe ventriculaire a l'aspect habituel, mais incidemment, toujours à la suite de diastoles prolongées, se voient des complexes d'échappement ventriculaire.

Le rythme nodal, après avoir évolué pendant les mois qui suivent sa création, se fixe donc et peut se reconnaître aux caractères que nous indiquons dans le paragraphe précédent. Leur valeur nous est certifiée par les examens histologiques pratiqués sur les pièces opératoires qui ont montré que la totalité du nœud sinusal avait été excisée.

KLEIN, M., et MAYER, G. (Strasbourg). Action du milieu péritonéal sur le testicule ectopique.

Grâce à une technique opératoire adéquate (cf. Klein et Mayer, 1942, *Arch. Physique Biol.*, t. 16, suppl. 61, pp. 133 et 135) on libère le

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feuillet pariétal de la tunique vaginale du testicule et on le retourne en doigt de gant sur la gonade mâle qu'on place en ectopie intra-abdominale. Cette opération a été pratiquée sur 21 rats et les animaux ont été sacrifiés en général entre 45 et 60 jours après l'intervention. A l'autopsie, on trouve le testicule enfermé dans le feuillet pariétal retourné qui lui constitue une enveloppe, libre de toute adhérence dans la cavité péritonéale. L'examen histologique révèle des tubes séminifères encore très peuplés, contenant tous les éléments de la lignée spermatogénétique, spermatogonies, spermatocytes avec des mitoses de maturation apparemment normales, spermatides. Mais le stade final de la spermiogenèse paraît troublé, puisqu'on ne trouve qu'exceptionnellement des spermatozoïdes complets avec flagellum. Si le testicule avait été en cryptorchidie simple selon la méthode habituelle, les tubes séminifères auraient été, après les mêmes délais, entièrement déshabités; on n'y aurait plus trouvé que le syncytium de Sertoli avec de rares spermatogonies.

En conclusion, dans un testicule en ectopie abdominale, mais qui est contenu dans le feuillet pariétal de la tunique vaginale retourné en doigt de gant, la lignée spermatogénétique est conservée, malgré la cryptorchidie; seule la spermiogenèse paraît troublée. Une action trophique directe du feuillet pariétal peut être exclue, puisque nous avons montré dans d'autres expériences que ce feuillet n'est pas indispensable à l'intégrité morphologique du testicule dans le scrotum. La vaginale retournée constitue donc une membrane protectrice contre l'influence nocive du milieu péritonéal. Ces expériences montrent que le facteur 'température' de la cavité péritonéale n'a pas l'importance que lui attribuent de nombreux auteurs dans les essais d'explication de la dégénérescence de la lignée spermatogénétique dans la cryptorchidie.

KNOWLTON, K., KENYON, A. T., LANDAU, R. L., and SANDFORD, T. (Chicago, Ill.). **Anabolic effects of the steroid hormones.**

Since the administration of synthetic testosterone propionate to patients suffering from testicular deficiency had resulted in body-weight gains for all, and appetite increase in some, as well as in the partial repair of their gonadal defects, the metabolic actions of this

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steroid were studied. Several eunuchoids were maintained in approximate balance on diets constant in composition for each individual throughout the study. Intramuscular injections of 25 mg. testosterone propionate were given daily for 8 to 14 days between a preliminary control period and a succeeding recovery period. In from 1 to 4 days after treatment began, urinary nitrogen excretion definitely decreased and remained at these lower levels until they returned to control values several days after treatment ceased. Creatinuria, whether spontaneous or established by creatine ingestion, followed a similar course; creatinine was unaltered. Urinary inorganic phosphorus, sulfur, potassium, sodium, chloride, and water usually behaved as did nitrogen. Amounts retained were greater than could be accounted for by increased genital tissue, hence an anabolic or, somatotropic effect had to be recognized. Similar studies in normal young men and women, and in men 76 years old, resulted in qualitatively similar findings, though only about half as much nitrogen, for example, was retained by them. Administration of this steroid to eunuchoids over much longer periods produced definite increases in urinary creatinine and in the basal metabolic rate, which was questionably affected in the shorter studies. Methyl testosterone, given orally, acted similarly except that creatinuria increased. Chorionic gonadotropin produced testosterone-like effects in a boy 13 years old, presumably due to stimulation of his own testes. Further studies on young adults with this material will be reported. Patients with adrenal insufficiency, diabetes, muscular dystrophy, and debilitation due to various conditions were able to respond characteristically to testosterone. Estradiol benzoate, 5 mg. injected intramuscularly daily, induced reduction in urinary nitrogen, inorganic phosphorus, sodium, and sometimes potassium in eunuchoids, a hypogonad, and a normal woman. Creatinuria and basal metabolic rate were unaffected. Androstene-dione given to two normal women caused slight reduction of urinary nitrogen and marked reduction of creatinuria in both, and retention of inorganic phosphorus in one; given to a man with adrenal insufficiency it diminished all three. Dehydroisoandrosterone did not affect the excretion of nitrogen, phosphorus, creatinine, or creatine in a woman with Cushing's syndrome nor in a hypogonad female dwarf.

LAMBERT, E. H., CODE, C. F., WOOD, E. H., and BALDES, E. J.
(Rochester, Minn.). **The effectiveness of man's cardiovascular adjustments to centrifugal force.**

Opinions regarding the relative importance of the hydrostatic effect of centrifugal force (positive acceleration) on the arterial as opposed to the venous side of the circulation have been varied. Early investigators, for the most part, believed that in the seated subject cardiovascular adjustments would be rendered ineffective by inadequate venous return and that with continued exposure to centrifugal force circulatory collapse would occur owing to pooling of blood below the heart. Observations on a modern human centrifuge have demonstrated that this is not the case and that effective cardiovascular adjustments are a uniform and striking occurrence.

Commencing with the onset of centrifugal force arterial pressure at head level falls progressively and after a characteristic latent period loss of vision or consciousness becomes evident at forces of 3.0 to 7.0 g. Several seconds after the onset of centrifugal force the progressive fall of arterial pressure is terminated and some recovery of pressure occurs even though the exposure is continued. In over 50% of instances this is sufficient to cause recovery from symptoms within 5 to 10 seconds.

The effectiveness of cardiovascular adjustments under these conditions is illustrated by the changes in arterial pressure at heart level. The average decrease in pressure per gm. increase in centrifugal force was only 4 mm. Hg. systolic and 0 mm. Hg. diastolic. The compensatory rise of pressure was from 20 to 70 mm. Hg. and began only 7 seconds after the force exceeded 1.5 g. (that is, 3 to 4 seconds before complete loss of vision occurred at forces which produced blackout). Loss of vision and consciousness would occur at accelerations considerably below the usual threshold if a progressive fall of arterial pressure occurred at heart level or if the compensatory rise were delayed.

The cardiovascular system is able to maintain arterial pressure and subsequently produce hypertension at heart level despite the fact that increased blood-flow and pooling of blood in the extremities continue during this sequence. As shown by plethysmographic studies, even the final amount of venous pooling after 45 to 60

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seconds does not embarrass cardiovascular function. Since arterial pressure does not fall significantly at heart level, the fall of pressure at head level with consequent occurrence of symptoms is due principally to the effect of increased weight of the blood on the arterial column between heart and head.

Observations in a specially instrumented dive-bomber have demonstrated that the cardiovascular adjustments observed on the centrifuge occur and are equally, if not more, effective during exposure to centrifugal force in aircraft.

LÜTHY, HERBERT (Bern). Ultraviolet absorption of the living nerve fiber.

The ultra-violet absorption of living nerve fibers of cold-blooded animals (frog and pike) is studied with the aid of an apparatus built after *Caspersson*,¹ *Lüthy*,² v. *Muralt*.³ The living nerve fiber has a very characteristic ultra-violet absorption: maxima at 265 mμ, 280 mμ, sometimes 302 mμ. Absorption at 265 mμ corresponds to the nucleotides, the thiamin, and cocarboxylase of living nerve. With the loss of excitability the absorption decreases over the whole range of the absorption curve. A new effect was described as ultra-violet dichroism. (*Lüthy*,⁴ *Lüthy and v. Muralt*.⁵) With polarisation parallel to the fiber-axis the extinction $\left(\log \frac{I_0}{I}\right)$ at 265 mμ is 3–10% higher than measured with light of the same wave-length with a plane of polarisation perpendicular to the fiber-axis. At 280 mμ the dichroism has the reversed sign, i.e. polarisation parallel yields an extinction 3–4% lower than polarisation at right angle. The studies of tabac mosaic virus⁶ and of thymonucleate films⁷ have shown that if the electric vector is perpendicular to the long axis of the molecule a selective increase in absorption is observed. The nucleotides, being oriented radially and the proteins in concentric layers in the myelin-sheath of nerve must yield an effect of reversal in sign of dichroism, as observed. The olfactory nerve of the pike has not a sheath with a protein structure and does not show the reversal of dichroism.

Stimulation of sectioned nerve and absorption measured near the cut shows the appearance of action-substances in the bathing solu-

tion (Ringer). Two maxima are observed at 260 $m\mu$ and 275 $m\mu$. Collecting the bathing solution of a stimulated nerve and an unstimulated control under identical conditions, shows that the cut surface produces an increased amount with stimulation of the intact nerve.

Stimulation of moniodoacetic acid poisoned nerve reverses the dichroism changes, developing with poisoning. A relation to accumulation of acetylcholine in poisoned nerve⁵ and disappearance of thiamin on stimulation of poisoned nerves exists. Normal aerobic nerves show no measurable changes with stimulation. Under anaerobic conditions, after each stimulation period a delayed and partly reversible change of ultra-violet absorption appears.

- ¹ Caspersson, T., *J. Royal micr. Soc.* 60, 8 (1940). ² Lüthy, H., *Helv. Physiol. Acta*, 4, C 20 (1946). ³ v. Muralt, A., *Die Signalübermittlung im Nerven*, Basel, 1946. ⁴ Lüthy, H., *Helv. Physiol. Acta*, 4, C 50 (1946). ⁵ Lüthy, H., and v. Muralt, A., *Schw. Med. Wschr.* 77, 10 (1947). ⁶ Butenandt, A., Friedrich-Freksa, H., Hartwig, S., and Scheibe, G., *Hoppe-Seylers Zschr.* 274, 276 (1942). ⁷ Caspersson, T., *Chromosoma*, 1, 605 (1940). ⁸ Wyss, A., and Wyss, F., *Exper.* 1, 160 (1945).

MACHEBŒUF, M. A., et GROS, F. (Paris). Recherches biochimiques sur l'action de la pénicilline et de la tyrothricine sur un microbe sensible à ces deux antibiotiques, clostridium sporogenes. Comparaison avec l'action sur certaines activités enzymatiques des extraits de muscles de mammifères.

Nous avons montré que la pénicilline inhibe considérablement la déphosphorylation de l'acide adénosine-triphosphorique par les suspensions non proliférantes de *Clostridium sporogenes*, même en présence de fluorure de sodium 0.06 M.

Cette action semble la seule sur le métabolisme phosphoglucidique du microbe, car la pénicilline n'inhibe pas l'hydrolyse de l'acide glycérrophosphorique ni la formation d'esters phosphoriques par le microbe à partir de glucose en présence de fluorure.

Or, la déphosphorylation de l'A.T.P. est une étape capitale du métabolisme dans le muscle des mammifères. Si la pénicilline était également capable de l'inhiber, elle devrait avoir une action considérable sur l'homme soumis à son action. Nous avons effectivement constaté que la déphosphorylation de l'A.T.P. par les extraits musculaires n'est pas inhibée par la pénicilline. Il faut penser que

l'enzyme n'est pas identique ou bien que les conditions de son action diffèrent. La tyrothricine n'inhibe pas la déphosphorylation de l'A.T.P. par les suspensions de *Clostridium*, elle ne réagit pas non plus sur la déphosphorylation par l'extrait musculaire.

MINZ, B., et PLOTKA, C. (Paris). La synergie des médiateurs chimiques en fonction du métabolisme des glucides.

L'antagonisme entre l'adrénaline et l'acétylcholine est loin d'être général. Les recherches des dernières années ont multiplié les exemples dans lesquels ces deux médiateurs agissent en parfaite synergie. Ce phénomène n'a pas seulement été observé dans des cas où les actions propres de ces substances se superposent, mais aussi au niveau d'organes réagissant primitivement à ces corps de façon antagoniste. C'est sur un pareil organe, l'intestin de lapin, que portent nos expériences. L'intestin répond à l'acétylcholine avec une contracture, à l'adrénaline avec un arrêt des mouvements spontanés et une diminution du tonus. Or, lorsqu'on ajoute de l'acétylcholine de 30 à 60 "après une addition préalable d'adrénaline, on constate un renforcement net de l'action acétylcholinique. Dans ces essais l'acétylcholine peut être activement remplacée par la choline et l'adrénaline le peut par l'adrénochrome. L'action conjuguée de l'adrénochrome ou de l'adrénaline d'une part, et de la choline de l'autre, fait apparaître dans le liquide baignant l'intestin, un corps dont l'effet sur la préparation de la sangsue est sensibilisée par l'ésérine. Elle entraîne donc l'apparition d'acétylcholine. Les résultats de nos recherches antérieures sur l'intervention de la co-carboxylase dans la synthèse du médiateur cholinergique, nous ont suggéré de chercher une solution 'métabolique' du phénomène de synergie enregistré. Nous avons ainsi trouvé que l'action indirecte de l'adrénaline et de l'adrénochrome vis-à-vis de la choline est exagérée par l'hexose-monophosphate, le pyruvate de sodium, l'adénosine-triphosphate et par la co-carboxylase elle-même. Une analyse détaillée de l'effet adrénalinique nous a apporté la preuve qu'il est entièrement dû à l'adrénochrome. L'adrénochrome exercerait cette action synergique en augmentant concurremment avec la co-carboxylase la formation de radicaux acétyl nécessaires à la synthèse de l'acétylcholine à partir de la choline.

MINZ, B., et VEIL, C. (Paris). La rigidité de décérébration implique-t-elle l'intervention d'un facteur humoral?

Chez un lapin en état de rigidité de décérébration l'enlèvement d'un segment important du nerf sciatique ne diminue que légèrement la rigidité de la patte correspondante. Une patte totalement éternée par section haute du sciatique et du crural, abolissant toute réponse réflexe dans ce membre et à partir de ce membre, laisse subsister une rigidité nettement perceptible. La diminution de rigidité, observée après section des nerfs, s'intensifie pourtant considérablement après ligature de l'artère fémorale correspondante.

Y aurait-il une substance chimique libérée par le centre lésé, véhiculée par le sang, et dont la présence conditionnerait la réaction hypertonique du muscle à l'excitation nerveuse?

Pour élucider cette question, nous avons essayé d'augmenter la concentration de ce corps hypothétique en réduisant la masse sanguine circulante par éviscération de l'animal. Nous avons observé que dans ces cas où la rigidité n'était pas absolue, elle pouvait être intensifiée à la suite de cette intervention. Dans les expériences effectuées sur un tel animal (en rigidité et éviscéré), sur lequel l'hypertonie musculaire était particulièrement intense, l'interruption momentanée de la circulation par pincement de l'artère iliaque au niveau de l'une des pattes provoquait une diminution nette du tonus des muscles. L'enlèvement de la pince était presque immédiatement suivi d'un rétablissement de la rigidité de cette patte, précédé d'une secousse musculaire localisée à ce niveau. Une ligature définitive de l'artère avait pour conséquence un relâchement quasi total du tonus. Nous avons excité mécaniquement la plaie au niveau de la section cérébrale chaque fois que nous avons observé une perte passagère et générale du tonus; immédiatement la rigidité se trouvait renforcée dans toutes les pattes, à l'exception de celle dont l'artère iliaque avait été préalablement liée. Notons que le pincement et le relâchement consécutif d'une artère iliaque chez un lapin normal n'entraîne aucune des manifestations enregistrées chez l'animal décérébré.

Nous avons constaté que le phénomène de rigidité s'accompagne d'une augmentation de la pression artérielle qui est sans rapport évident avec la manifestation de celui-ci. Cette hypertension n'est

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pas due à l'effet mécanique de l'hypercontraction; car elle subsiste quand, sous l'action du curare, l'animal tombe en état de résolution musculaire complète. Nous avons d'autre part constaté que le 933 F, considéré comme le sympathicolytique le plus couramment utilisé, abaisse la pression artérielle à son niveau initial et même au-dessous; il abolit en même temps, tout comme le curare, la rigidité de décébration; celle-ci réapparaît avec l'élimination du 'sympathicolytique'.

MONNIER, M. (Zürich). L'électro-rétinogramme (ERG) de l'homme.

Les manifestations électriques de l'activité rétinienne ont été encore peu étudiées chez l'homme à cause des difficultés techniques auxquelles se heurte l'expérimentateur. Avec notre collaborateur F. Boehm, nous avons mis au point une technique d'électro-rétinographie périmétrique qui nous a permis d'étudier, chez l'homme, les variations de l'ERG selon l'endroit de la rétine éclairé, l'intensité du stimulus lumineux, sa couleur et l'état d'adaptation de la rétine. Par ailleurs nous avons enregistré les manifestations bioélectriques consensuelles de la rétine, les réactions simultanées de la rétine et du cerveau (ERG + EEG), enfin certaines manifestations pathologiques dans des cas de troubles de la vision (Monnier et Boehm, *Helv. Physiol. Acta*, 1945; Monnier et Amsler, *Ophthalmologica*, 1945; Monnier, *C. R. Soc. Biol.*, avril 1946; *Experientia*, 1946; Monnier et Jeanneret, *Ophthalmologica*, 1947).

Technique: Le sujet est assis devant un périmètre dont l'arc gradué porte un dispositif d'éclairage (lampe, diaphragmes, lentille, filtres de couleurs). Ce dispositif mobile permet de projeter un spot lumineux sur les divers secteurs de la rétine et d'en régler l'intensité, la durée, la couleur. La stimulation intermittente (flicker: 1 éclair par sec.) a l'avantage de réaliser des conditions d'adaptation rétinienne et pupillaire constantes. Les potentiels rétiens sont dérivés à l'aide d'électrodes impolarisables (type Monnier et Boehm), l'une en contact avec la cornée, l'autre fixée à la tempe. Ils sont amplifiés 2 millions de fois et enregistrés à l'aide d'un oscillographe cathodique.

Résultats: L'analyse de plus de 1800 tracés chez l'homme a permis de faire les constatations suivantes:

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1. Les critères les plus sûrs de l'ERG sont la latence du potentiel *b*, la durée de sa phase ascendante (Gipfelzeit) et son amplitude (50 à 300 microvolts). A ce potentiel positif succède souvent une déflexion négative qui correspond à la contraction de l'iris, comme le prouve un film des réactions pupillaires à la lumière ultra-violette. Le potentiel *c* qui suit est faible ou absent normalement, mais exagéré dans certains cas d'affection cérébrale.

2. La stimulation de la région centrale de la rétine (20°) raccourcit les temps et augmente l'amplitude du potentiel *b*; la stimulation de la rétine périphérique (60°) a une action inverse. L'électro-rétinographie périmétrique permet donc de contrôler objectivement le champ visuel.

3. L'augmentation d'intensité du stimulus lumineux raccourcit également les temps et augmente l'amplitude du potentiel *b*.

4. L'électro-rétinographie binoculaire révèle que l'éclairement d'un seul œil produit une réaction consensuelle, assimilable au potentiel *c*, à l'œil non éclairé.

5. La stimulation de la rétine avec des spots lumineux de couleurs différentes provoque des variations caractéristiques de l'ERG.

6. L'enregistrement simultané de l'ERG et EEG permet de mesurer le 'temps central'. Cette valeur qu'on obtient en déduisant du temps de blocage du rythme la latence du potentiel rétinien *b*, nous renseigne sur la conductibilité des voies optiques centrales. Elle augmente dans les cas de lésions du nerf optique.

MORICARD, R. (Paris). **Déclenchement hormonal de la maturation ovulaire chez la lapine et chez la rate hypophysectomisée (Fonction méfogène du liquide folliculaire).**

Chez les Mammifères l'ovule termine sa 1^{ère} mitose réductionnelle quand il flotte dans le liquide folliculaire. Chez la lapine, c'est le coït qui déclenche la formation du 1^{er} globule polaire précédant l'ovulation.

En 1933-4, j'ai montré que chez la lapine, l'injection de gonadotrophine déclenche en 7 heures la disparition de la vésicule germinative avec différenciation complète de la métaphase de 1^{ère} mitose de maturation précédant immédiatement la formation du 1^{er} globule polaire à laquelle succède l'ovulation.

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Cette étude n'avait pas été abordée par les endocrinologistes qui se sont occupés des hormones sexuelles de 1921 à 1933, en particulier par *Evans et Long* (1921), *Zondek* (1926), *Aschheim* (1926), *P. E. Smith* (1926), *Friedmann* (1929), *Parkes* (1929), *Courrier* (1929), *Smith et White* (1931), *Selye* (1933), *Hinsey et Markee* (1933). Certaines remarques formulées à ce propos par *Courrier* en 1946 à la Société de Biologie sont donc erronées.

Nos résultats furent confirmés, indépendamment, par *Pincus* en 1935 et repris par *van Ravensteyn* en 1945 sur la souris puis par *Samuels* en 1946.

Chez la rate 'hypophysectomisée' d'après *P. E. Smith*, il y a encore formation du 1^{er} globule polaire. Nous avons vérifié sur 120 rates 'hypophysectomisées' que cette observation est exacte mais l'interprétation en est probablement erronée, car dans l' 'hypophysectomie' de *Smith*, on laisse systématiquement la pars tuberalis. Il n'est donc pas possible d'affirmer que l'hypophysectomie est complète et qu'il y a indépendance entre l'ovogenèse et la fonction hypophysaire comme l'ont admis *Swezy* (1933) et *Zondek* (1935). Il y a dans la pars tuberalis des cellules endocriniennes non négligeables. Nous avons essayé d'enlever l'hypophyse et la pars tuberalis, mais la survie des animaux n'a pas dépassé quelques semaines.

On est conduit à penser que dans les conditions physiologiques, il existe des relations de causalité entre une variation de la charge hormonale du liquide folliculaire, et la formation du 1^{er} globule polaire pendant l'ovulation.

Ce résultat oblige à réviser la notion de la fonction œstrogène du liquide folliculaire telle qu'elle semblait établie à la suite des travaux d'*Allen et Doisy* (1923) repris par *Courrier* en 1924.

Le liquide folliculaire aurait une fonction méiogène.

VON MURALT, ALEXANDER, and LÜSCHER, E. (Bern). The neuro-regenerative factor 'NR'.

Brain, spinal cord, myelinated nerves, and thymus contain a dialyzable factor, increasing the speed of outgrowth of new fibres and decreasing the latency of regeneration of cut and degenerated nerves in the cornea of the rabbit. This factor is obtained from young animals and is not specific for any species. We have called it the

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neuro-regenerative factor 'NR'. NR exists in brain, mainly in the white matter in a bound form, from which it is freed by enzymatic activity; it passes a dialyzing membrane in very short time and can be concentrated from the dialysate by evaporation in vacuo. 1 c.c. of the final solution, corresponding to 1 mg. of fresh brain, is injected intraperitoneally and daily and produces 7-9 days after operation the onset of regeneration in the cornea. The highest activities of brain dialysates with regard to NR were found in April and May. If 1 c.c. of saline is injected in the same way, regeneration only begins after 17 days in the period March-August and after more than 20 days from September-February. The cornea test is carried out as follows: fine circular cut of cornea down to Descemet's membrane (percaïne anesthesia), control of degeneration of all cornea nerves 4 days after operation by touch tests with test-hair and vital staining (methylene blue) and slit-lamp. With regeneration, a distinct sensitive area within the scar is recognized, by evoking lid-reflex. Treated animals show throughout higher acetylcholine content of operated cornea than all controls. Successfully treated animals have between the 10th-20th day after operation an acetylcholine content of the operated cornea 30-50% higher than untreated controls. Already several hours after operation, the denervated cornea shows a marked fall in acetylcholine content, reaching a minimum of 20% normal on the 10th day.

Active dialysates show a very characteristic ultra-violet absorption-spectrum with a maximum at 248 $m\mu$.

NOLF, P. (Brussels). L'A-fibrinogène de Wooldridge.

Refroidi à 0° C., le plasma du chien qui a reçu une injection intraveineuse de peptone se trouble et laisse déposer une substance protéique, qui se redissout par le réchauffement à 37° C. Elle a été isolée par Wooldridge et désignée par lui sous le nom d'A-fibrinogène. Elle est présente dans le plasma normal des mammifères et peut en être séparée à l'état de purté.

Elle exerce une action coagulante sur tous les plasmas de mammifères qu'un traitement approprié a rendus spontanément incoagulables, sans les priver de leur prothrombine, tels que le plasma de cheval filtré à 0°, le plasma adsorbé sur oxalate calcique colloïdal, etc.

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En présence de l'ion Ca, l'A-fibrinogène est dénué de toute action coagulante sur la solution de fibrinogène et sur le plasma phosphaté (ou sur la solution de fibrinogène additionnée de thrombogène). Par contre, il coagule le plasma phosphaté qui a été additionné de thrombozyme ou un mélange spontanément incoagulable de thrombozyme, de thrombogène et de fibrinogène. Autrement dit, son activité coagulante exige, pour s'exercer, la présence simultanée de la thrombozyme et du thrombogène, couple fonctionnel connu sous le nom de prothrombine dans la théorie classique de la coagulation.

Le rôle de l'A-fibrinogène est de favoriser l'union de la thrombozyme et du thrombogène, dont le produit est la thrombine. Il appartient donc à la catégorie des agents thromboplastiques; il est une protéine thromboplastique, autrement dit, une thromboplastine. Pur, il n'exerce aucune action protéolytique sur le fibrinogène.

Traité par l'alcool éthylique à la température ordinaire, il est décomposé en un résidu insoluble de protéine dénaturée, qui est dénué d'activité coagulante et en une fraction phospholipidique soluble dans l'alcool, qui est thromboplastique.

O'CONNOR, J. M. (Dublin). *The influence of temperature on oxygen consumption in relation to the constancy of body temperature.*

The influence of temperature on oxygen consumption of animal tissues has been believed to be a continuous increase with rising temperature but in fact the rise is interrupted (above 18° C.) by two falls, one at about 30°, the second at 35.5°-42°. These falls are inherent in the mechanism of animal oxidation. The second of them is fundamental in the fixation of body temperature in homoiothermal animals, and is responsible for the maintenance of a constant temperature in animals in which the centres have been put out of action. The falls are associated with the disappearance from a monomolecular layer of fatty acids on an undetermined surface of, in the first instance, oleic acid and, in the second, palmitic acid.

The evidence now to be presented is as follows:

(a) The oxygen consumption of the skin of the finger (determined by the time of disappearance of the oxyhaemoglobin band) when graphed against temperature shows the two falls.

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(b) The pattern of this graph is altered in a predictable manner if the skin has been treated previously with a particular fatty acid.

(c) The oxygen consumption of the isolated skin of the frog shows the falls. The extent of the second change in level corresponds with the proportion of palmitic to stearic acid in the fat of the frog.

(d) The oxygen consumption of the isolated cornea of the ox shows a similar pattern. The extent of the second fall is again proportional to the palmitic: stearic ratio of ox fat.

(e) The oxygen consumption of the gastrocnemius muscle of the spinal cat (data of *Freund* and *Jannsen*) graphed against muscle temperature shows a sharp fall at a temperature near to the normal body temperature.

OVERBEEK, G. A. (Oss, Holland). **Muscular fatigue in normal and adrenalectomized rats.**

The influence of adrenalectomy on the work performance of rats was studied by the method of *Everse* and *de Fremery*. Only male rats (150–200 gr.) were used, not later than one week after adrenalectomy. The diminished effect of repeated electrical stimulation, which is observed in adrenalectomized rats, is not caused by the accumulation of lactic acid in the stimulated muscle, although such accumulation was observed. It was supposed that the transmission of nervous impulses might be impaired. In fact the decreased performance of adrenalectomized rats could be increased to normal by the injection into the muscle of physostigmine or doryl, but not of acetylcholine or adrenaline. The fact that acetylcholine produces no well-defined effect might be explained by its rapid destruction by the cholinesterase of muscle. Six days after sectioning the sciatic nerve, when acetylcholine is no longer produced by the degenerated nerve, the same decreased work performance as in adrenalectomized rats was observed. A shortage of acetylcholine after adrenalectomy could be caused either by a decreased production or by an increased destruction. The injection of citric acid into adrenalectomized rats, which is reported to increase production of acetylcholine, had no significant effect. The injection into normal rats of vitamin K, which is reported to decrease production of acetylcholine, also had no such effect. On the other hand the blood serum of adrenalectomized rats showed no

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increased cholinesterase activity. At the moment no arguments exist in favour of one or the other hypothesis. The same decreased muscular performance as after adrenalectomy or after degeneration of the sciatic nerve could be observed during the first week after hypophysectomy, during shock of various origin, and in thyroid insufficiency. These facts justify the supposition that the causes of the asthenia in adrenal insufficiency should be sought in the transmission of nerve impulses rather than in the muscle itself. However it must be stressed that this refers only to the first week after adrenalectomy. Indications exist that in a later phase changes in the muscle might occur.

PAESI, F. J. A. (Leyden). *Some aspects of follicle growth in the ovary.*

Oestrogens are known to induce in the ovary of the *hypophysectomized* rat the formation of a large number of medium-sized follicles. The latter are provided with a thick granulosa, and possess no cavity. Under the influence of testosterone this granulosa dissociates into single cells. In a *normal* animal testosterone strongly favours the development of the follicular cavity. Both phenomena may rest on a common base, namely a decrease of the cohesion between the granulosa cells caused by the combined action of oestrogen and androgen. It is thinkable that the normal development of the cavity is due to the distension of the weakened granulosa under the influence of the pressure exercised by the liquor folliculi. Other arguments for this interpretation were derived from our experiments with regard to the Collip-effect.

The required amount of androgen may be produced in the ovary; we could show that in hypophysectomized rats androgen is liberated when the interstitial tissue is stimulated by placental gonadotrophin.

We measured all follicles and corpora lutea in ovaries of hypophysectomized rats and of normal mice (some of these treated with gonadotrophin) and divided them on account of their *diameter* in size classes with a class interval of 10μ . The various size-distribution-curves exhibit a striking similarity in form: after a steep descent they all show a nearly asymptotic approach to the horizontal. This could not be ascribed to a gradually decreasing degree of atresia, but a plausible explanation was found in the assumption that in each unit

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of time the growth of the follicle is proportional to the volume that the follicle at that moment has reached. This is in agreement with the observations of *Lane* and *Davis* with regard to the number of mitoses per unit of volume. The shape of the curves and the large number of mitoses plead for a normal growth rate in the follicles of the hypophysectomized rats.

The hypophysis appears to be more essential for the subsequent development of the primordial follicle (ovum with a single layer of granulosa cells) than for the preceding development of the ovum into the primordial follicle. So in the hypophysectomized animal the number of primordial follicles grows even larger than in the normal one! Placental gonadotrophin checks this increase and retards the further development of the follicle; these effects may be due to the activity of androgen of which the production was stimulated by the administration of gonadotrophin, for androgen checks the development of the young egg cells.

PETITPIERRE, CL. (Lausanne). L'Amélioration de la valeur alimentaire des farines de céréales.

Des essais sur de jeunes rats en croissance ont permis de montrer que, administrées ad libitum et complétées par des sels minéraux et de la vitamine D, des farines de blé d'un taux d'extraction variant de 70 à 100 % provoquent des croissances pratiquement identiques. En complétant ces régimes par des germes de blé, du lait en poudre ou de la levure de bière, de façon que l'augmentation du taux protéinique soit identique dans tous les cas, nous avons obtenu les résultats suivants: Les germes de blé n'améliorent pas la croissance; même complété par la lactoflavine, ce régime enrichi en germes ne produit qu'une croissance de peu supérieure à celle du lot témoin. Le lait en poudre et la levure de bière améliorent considérablement la croissance, la levure semble-t-il un peu plus que le lait. Le complément simultané par le lait, la levure et les germes provoque une croissance encore plus rapide que la levure seule. Cette amélioration de la croissance doit être due bien plus au fait que le déficit en acides aminés des céréales sont comblés par la levure et le lait, qu'à un complément en vitamines. En effet une adjonction de 0.1 % de caséine et de 0.2 % de levure suffit déjà à améliorer nettement la

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croissance, qui atteint l'optimum avec 0.25 % de caséine et 0.5 % de levure.

PI SUÑER, A., CARTAYA, J. A., SOTO RIVERA, A., and GALÍNDEZ, H. (Caracas, Venezuela). **The influence of uremic blood upon the urea clearance.**

Since a long time ago and on repeated occasions, we had been able to demonstrate that the blood of nephrectomized animals have an influence upon the diuresis by others. This effect is accomplished by the substances that accumulate in the body fluids of uremic animals. If the concentration of these substances is not too great, they produce an increase in the secretion of urine.

Trying to clarify the mechanism of this phenomenon, we recently studied the influence of uremic blood upon the urea clearance and the relation between urea clearance changes and the modifications of the diuresis. We determined the clearance value using *Austin, Stillman*, and *Van Slyke's* formula¹ for the standard clearance. *Ralli, Brown*, and *Pariente*², *Jolliffe* and *Smith*³ showed that it is possible to apply it to the renal excretion of urea in the dog. The body surface of the dog has been calculated with *Benedict's* formula.⁴

In the blood from double nephrectomized dogs, taken 36 to 48 hours after the operation, the urea was determined. The various amounts in terms of urea: twelve to thirty milligrams were given per kilo of body weight. Under these circumstances there is an increase of diuresis but the urea clearance practically remains unchanged, being very small in its modifications.

The specific gravity of urine is not changed either, which shows that substances different from urea are being eliminated. In a few experiments we have found that there is an increase in creatinine excretion, but the results are not yet conclusive in view of the small number of observations.

It is significant that the administrations of uremic blood in the dog is not followed by an increase of urea clearance, but by the increased water elimination accompanied by substances of high molecular weight.

¹ *Journ. Biol. Chem.* 46, 91 (1921). ² *Am. Journ. Physiol.* 97, 432 (1931).

³ *Am. Journ. Physiol.* 98, 572 (1931). ⁴ *Ergebn. Physiol.* 36, 300 (1933).

POLONOVSKI, M., BUSNEL, R., et CHAUCHARD, P. (Paris).

Vicariance de la vitamine B 1 par l'acide folique et la xanthoptérine chez le rat et le pigeon.

Nous avons montré que certains dérivés ptériniques naturels ou de synthèse (fluorescynanine, xanthoptérine, isoxanthoptérine, acide isoxanthoptérine carboxylique, acide ptéroylglutamique, etc.) peuvent, chez le rat et le pigeon, suppléer à une carence alimentaire totale en aneurine ou en riboflavine.¹

D'autre part,² nous avons mis en évidence le rôle de certains de ces composés dans la respiration cellulaire des mélanocytes de l'écaille de carpe et dans le catatorulin-test, où ils avaient une action vicariante de l'aneurine.

Nous nous sommes cependant demandé si l'action physiologique constatée dans la croissance du rat et du pigeon était liée à une symbiose bactérienne intestinale, comme pouvait nous le faire penser le résultat des travaux de *Totter et Day*,³ d'*Elvehjem* et al.⁴

Expérimentant sur des rats coecumectomisés,⁵ nous avons pu constater une certaine diminution de croissance par rapport aux rats normaux, dans l'action vicariante de nos ptérines pour l'aneurine, plaidant en faveur d'une action vitaminique indirecte par synthèse bactérienne aux dépens des noyaux ptéridiniques.

Nous avons cherché à confirmer ces expériences en soumettant à l'action des ptérines des pigeons au régime d'avitaminose B 1 en présence du sulfaguanidine.

A cet effet, des lots de pigeons furent soumis au régime d'avitaminose B 1 de Randoïn-Lecoq, complété pour certains par 1 % de sulfaguanidine.

Les crises de polynévrite se manifestèrent au bout de 16 à 20 jours sans différence nette attribuable à la présence de la sulfamide, et sans que la température des animaux, ni leur taux de leucocytes, soient diversement affectés.

Les pigeons reçurent ensuite les ptérines à des doses de 30 γ et 100 γ pro die pour la xanthoptérine, 50 γ et 100 γ pour l'acide folique.

Au bout de 16 jours, l'augmentation moyenne de poids s'établit comme suit:

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			Nb. de Gain pigeons
		gm.	
Régime d'avitaminose	+ 50 γ acide folique	35	5
"	" + 100 γ " " " + guanidine	34	3
"	" + 30 γ xanthoptérine	34	3
"	" + 100 γ " " + guanidine	39	3
"	" + 20 γ aneurine + " "	28	2

Les températures de tous les animaux redeviennent normales, ainsi que les chronaxies, le taux des leucocytes, les glycémies et les indices chroniques résiduels plasmatiques.

L'examen du tube digestif des pigeons ayant reçu la sulfaguanidine ne révèle pas de modifications quantitatives nettes de sa flore bactérienne.

Il se dégage de cette expérience que, chez le pigeon, l'action de la sulfamide, sans affecter quantitativement la flore intestinale et sans accélérer la carence vitaminique B₁, ralentit l'action vicariante de l'acide folique et de la xanthoptérine, si l'on tient compte du fait que des doses doubles et triples de ces substances ne déterminent pas chez les pigeons sulfamidés, d'accroissement plus notable que des doses simples chez les témoins.

L'action physiologique des ptérines semble donc, dans une certaine mesure, chez le pigeon comme chez le rat, en rapport avec le métabolisme propre de la flore intestinale.

¹ Busnel, R. G., Chauchard, P., Mazoue, H., et Polonovski, M., *C. R. Acad. Sci.* **224**, 237 (1947). ² Busnel, R. G., Polonovski, M., et Pesson, M., *Helvetica Chimica Acta*, **39**, fasc. 5 (1946). ³ Totter, J. R., et Day, P. L., *J. Biol. Chem.* **147**, 257 (1943). ⁴ Elvehjem, C. A., et Beverly, Ransome, J. *Biol. Chem.* **151**, 109 (1943). ⁵ Benard, H., Busnel, R. G., Chauchard, P., Mazoue, H., et Polonovski, M., *C. R. Acad. Sci.* **223**, 826 (1946).

RANZI, SILVIO (Milano). Proteins and embryonic development.

There are two alterations which are obtainable in the embryonic development of Amphibia. In embryos, which are developing in lithium chloride (sodium sulphate, sodium chloride, sodium tartrate, ethyl alcohol, etc. induce the same, but less pronounced, deviation), the notochord is smaller and thus an hypoevocation (namely cyclopia). Instead in embryos, which are developing in sodium thiocyanate (sodium iodide and vital dyes induce the same,

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but less pronounced, deviation), the notochord is abnormally large and we can observe phenomena of hyperevocation (myelencephalon larger, a large mass of neural cells is in the roof of the fourth ventricle, the pineal body is double).

These two kinds of alterations correspond to the well-known vegetalisation and animalisation of the echinoderm embryo.

I have studied if these effects of the different substances on embryo determination can be related to changes of the proteins induced by the employed chemical agents. The whole extract of embryos of Amphibia and the fractions containing Needham's euglobulin *b* or Szent-Gyorgyi's structure proteins 1 (fractions containing proteins which are or can easily appear fibrillar) show a decrease in viscosity when treated with sodium thiocyanate in the same concentration which induces the notochord increase. Sodium iodide and pyrocyanine induce the same effect on the whole extract and on the fractions. The lithium chloride, as well as all the chemical substances which induce cyclopia, increases the viscosity of all these extracts. The extracts of embryos containing only proteins which are not fibrillar show an increase in viscosity as the effect both of lithium chloride and of sodium thiocyanate (or of all other salts); the vital dyes are practically without effect. Some preliminary determinations show similar results on protein extracts from sea-urchin eggs.

These findings are probably related to the shape of the particles. Myosin solutions from rabbit or pigeon and thymonucleic acid solutions from pancreas of oxen in presence of sodium thiocyanate, sodium iodide, methylene-blue show a decrease in viscosity when these chemical substances are in the concentrations which induce increase of the notochord and hyperevocation in Amphibia and animalisation in Echinoderms. The myosin solution shows increase in viscosity when treated with the same chemical substances in stronger concentrations or with lithium chloride and other chemicals inducing cyclopia. All the employed chemicals always induce an increase in viscosity of the solutions containing spherical particles as globulin X or gelatine gold brand.

These researches show that the two kinds of substances which influence, in opposed ways, the embryo development of Amphibia and sea urchins, induce, the first a decrease, the second an increase, in viscosity of fibrillar protein solutions. Bearing in mind that

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changes in embryo determination are induced by those chemical substances, our investigation might point out that proteins which are or can easily appear fibrillar (as euglobulin *b* of Amphibian embryo) are responsible for such changes.

RIJLANT, P. (Brussels). La Respiration 'occulte' du centre respiratoire fondamental après la destruction du centre modulateur.

Chez le lapin et le chat, curarisés ou non, et anesthésiés au chloralose ou au nembutal, des destructions limitées du tissu nerveux, au niveau de l'obex, déterminent la disparition complète ou presque complète, de toute activité à systématisation respiratoire dans les nerfs phréniques, intercostaux et récurrents. Cet effet n'est obtenu pour des destructions très limitées, que lorsque celles-ci sont réalisées dans la profondeur du tissu nerveux, sur la ligne médiane, à l'aplomb de l'extrémité postérieure du plancher du quatrième ventricule. La lésion est, soit une incision sagittale profonde ou une électrocoagulation; dans quelques expériences la polarisation électrique a aussi permis d'obtenir la disparition transitoire de l'activité respiratoire. En général la destruction doit s'étendre sur une hauteur de 5 mm.

Dans quelques expériences l'asphyxie de l'animal a amené le retour transitoire d'une activité respiratoire dans les nerfs phréniques, cet effet disparaissant dès le rétablissement d'une ventilation pulmonaire normale.

L'excitation électrique, à la fréquence de 50 à 150 par seconde, des neurones d'origine des nerfs phréniques, récurrents ou intercostaux, installe dans ces nerfs des ripostes qui présentent une systématisation respiratoire nette.

L'effet obtenu est homolatéral et n'intéresse en général que les neurones directement excités. Dans quelques expériences des ripostes ont apparu à des niveaux inférieurs à l'excitation.

La réponse à systématisation respiratoire est remplacée par une réponse continue dès que l'intensité d'excitation est suffisamment augmentée. Dans deux expériences l'activité respiratoire n'a disparu que d'un côté et s'est maintenue partiellement de l'autre. La réponse à l'excitation continue infraliminale des neurones moteurs inspireurs du côté apparemment inactif a provoqué des réponses coïncidant

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complètement avec l'activité inspiratoire spontanée du côté opposé.

Le territoire nerveux détruit dans toutes ces expériences coïncide avec le 'centre modulateur' dont l'excitation, sans provoquer par elle-même d'activité inspiratoire, impose cependant à celle-ci le rythme d'excitation.¹

De ces expériences on peut conclure à la persistance des mécanismes centraux responsables de l'élaboration de la rythmicité respiratoire après la lésion bulbaire limitée, seule l'extériorisation motrice étant supprimée. En rétablissant celle-ci par l'excitation infraliminale directe des neurones moteurs l'intégrité des voies qui connectent le mécanisme respiratoire primaire à ces neurones et moteurs est démontrée.

La transformation de la respiration en une activité 'occulte' par la lésion bulbaire ne peut ainsi traduire que la perte d'un appoint renforteur prenant son origine dans l'activité du territoire modulateur. La respiration physiologique dépend ainsi de la sommation, au niveau des neurones moteurs des nerfs phréniques, récurrents, intercostaux, etc. de stimuli leur parvenant au départ de deux centres, l'un responsable de l'établissement du rythme et de la durée de l'inspiration — mais dont l'intervention isolée ne parvient pas à activer les neurones moteurs, la respiration restant ainsi occulte — tandis que l'autre assure l'efficacité de la stimulation en imprimant son rythme propre dont la fréquence est d'environ cent par seconde.

¹ Rijlant, P., *Acad. roy. méd. Belgique. Mémoires* 1942, 1, fasc. 10.

SCHEINER, H. (Paris). **Poisons de l'élasticité musculaire.**

Le muscle droit de l'abdomen de la grenouille, fraîchement isolé, est relativement peu sensible à l'acétylcholine; cependant, lorsqu'on conserve le muscle, pendant un temps plus ou moins long, à la température de 4°-10°, sa sensibilité à l'acétylcholine va croissant. Si l'on observe le comportement de l'excitabilité électrique parallèlement à l'augmentation de la réponse acétylcholinique, on constate sa diminution progressive. Ainsi, un muscle conservé pendant 10 jours à la glacière, présentait une sensibilité à l'acétylcholine 10 fois plus grande qu'au moment du prélèvement alors que sa contractilité électrique était totalement disparue.

D'autre part, nous avons constaté que les narcotiques, alors qu'ils

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abaissent ou suppriment l'excitabilité électrique du muscle droit, exaltent sa réponse acétylcholinique. Ainsi la sensibilisation obtenue par uréthane est environ deux fois plus intense que celle obtenue par éserine.

Enfin, nous avons vu que la fatigue du muscle, réalisée par l'action d'une série de chocs d'induction maximales et poursuivie jusqu'à l'épuisement complet du muscle (arrêt des secousses) produit également une sensibilisation à l'acétylcholine comparable à celle obtenue par les narcotiques.

La modification commune que le muscle subit au cours de l'usure (conservation), dans la fatigue, comme dans la narcose consiste en une perte d'élasticité qui se traduit par l'allongement du muscle (jusqu'à 20-25 % de sa longueur initiale) ainsi que par l'augmentation de sa plasticité. (Un tiraillement exercé sur le muscle a pour conséquence un retour très lent du muscle à sa longueur d'avant le tiraillement.)

La perte de l'élasticité du muscle que nous constatons au cours de nos expériences est en grande partie réversible. En effet, il suffit d'une très petite quantité d'acétylcholine (0.1 γ -1 γ) pour faire reprendre au muscle sa longueur initiale et son élasticité (résistance au tiraillement).

En même temps que l'on constate, par suite de l'administration d'acétylcholine, une augmentation de l'élasticité déprimée par la fatigue ou par la narcose, on voit réapparaître l'excitabilité électrique abolie. Ainsi, après l'établissement d'une course de fatigue, aboutissant à la suite de 2000 chocs d'induction, se succédant à un intervalle de 2 secondes, à une chute de l'élasticité comparable au relâchement du tonus d'un muscle lisse traité par adrénaline ainsi que, en même temps, à l'arrêt complet des réponses électriques, l'addition au bain où le muscle est suspendu de 0.5 γ d'acétylcholine a pour conséquence la reprise des réponses électriques. La force musculaire ainsi rétablie par acétylcholine atteint en quelques minutes 80 % de la force initiale du muscle.

Toutefois, la force du muscle ainsi restaurée n'est pas un simple retour à l'excitabilité normale d'avant l'expérience de fatigue. Elle se distingue par les faits suivants:

1. Elle ne survient qu'en présence d'oxygène (oxygénation du Ringer);

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2. Elle est susceptible de se renforcer après administration de dérivés puriques et tout particulièrement de caféine, qui, par elle-même, n'a aucune action sur la force et sur l'excitabilité du muscle isolé.

3. Enfin, le muscle fatigué qui, sous l'action d'acétylcholine, travaille apparemment comme un muscle directement excité, est très sensible à l'action du curare et de la strychnine. En effet, l'addition au bain de 0.05 mg. de curare ou de 0.1-0.5 mg. de sulfate de strychnine supprime immédiatement l'excitabilité électrique du muscle.

Ainsi, le muscle épuisé par une longue série d'excitations directes et dont les contractions réapparaissent sous l'effet d'acétylcholine se comporte à plusieurs égards comme un muscle excité par l'intermédiaire de son nerf.

Conclusion: Nos expériences montrent que l'élasticité du muscle est une propriété complexe. A côté de la visco-élasticité, due aux propriétés physico-chimiques structurales de la substance musculaire, il y a lieu d'admettre une élasticité physiologique analogue sinon identique au tonus de la musculature lisse. Il est possible que le maintien de cette élasticité soit assuré par des éléments nerveux autonomes situés dans le muscle. Le rapport de discordance et, en même temps, de relation réciproque entre la contractilité électrique et la sensibilité acétylcholinique semble indiquer l'existence de deux mécanismes de la contraction musculaire, que l'analyse pharmacodynamique permet de dissocier.

SCHÜTZ, F. (Birmingham). The reaction of urea \rightleftharpoons ammonium cyanate in cells, and some pharmacological actions of cyanate.

It was found that cyanate combined with methaemoglobin, haem and proto-porphyrin, giving characteristic shifts of absorption bands. One molecule of cyanate combines with one of methaemoglobin. While CN was found to have greater affinity for met-Hb than CNO, the latter inhibited formation of Hb-F. CNO is thus capable of combining with Fe in met-Hb, and also with iron-free porphyrin. It prevents aggregation and precipitation of these pigments. It reacts with serum proteins, markedly raises the heat coagulation

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point, and increases the rate of ultrafiltration of serum. Serum containing >0.16 M cyanate does not coagulate on boiling, although the reaction of the solution remains at pH 7.4 (phosphate buffer). It has marked diuretic and feeble narcotic action in rats, and is of low toxicity (CN:CNO = 1:60). It had a slight deepening and slowing effect on respiration in the decerebrated cat, practically no effect on blood pressure in spinal and decerebrated cats and rabbits under ether. Neither was the isolated heart, gut and uterus affected by small and medium doses.

If injected into nephrectomised animals it raises the degree of oxygenation of venous blood. Its activity as inhibitor of cell respiration is also evident with tissue slices respiring in a protein free medium (CN:CNO = 1:40). If respiring in serum, however, the effect was small or nil, because serum proteins successfully compete for CNO. Cyanate was found to combine with cytochrome a3, but not with cytochrome c. Details of its actions on tissue metabolism will be discussed.

Strong indication for the formation in cells of NH_4CNO was obtained by two methods which will be discussed in detail. They involve reconversion of NH_4CNO into urea and distillation *in vacuo* of cyanic acid from lysed cells under special conditions. Small amounts were regularly found in cells. Much larger amounts were found after nephrectomy and water retention. This would theoretically be expected when, on dilution, the thermodynamic equilibrium between the dissociated (cyanate) and undissociated (urea) components is shifted in favour of the former. A possible role of cyanate in the regulation of water balance will be discussed in this connexion.

Schütz, F., *Nature*, 155, 759 (1945). Schütz, F., *J. Physiol.* 105, 17 P (1946). Birch, K. M., and Schütz, F., *Brit. J. Pharmacol.* 1, 186 (1946). Cumming, G., and Schütz, F., in the press. Dirnhuber, P., and Schütz, F., in the press.

SPERBER, IVAR (Uppsala). The mechanism of renal excretion of some 'detoxication products' in the chicken.

The excretion of several substances, particularly some so-called 'detoxication products', has been investigated in chickens. A method previously outlined by the author (*Nature*, 158, 131) has been used.

This is based on the existence of a renal portal circulation in birds. The difference between the amounts of a substance excreted by the two kidneys is determined, after the injection of the substance into one leg. This difference is nil for substances excreted by filtration only (ignoring possible effects due to diffusion). For substances excreted by the tubules a difference is found, which is more pronounced, the more efficient the tubular excretion mechanism.

Hippuric acid and ornithuric acid are both excreted by the tubules. Benzoic acid is not. *p*-Acetylaminobenzoic acid is excreted by the tubules, but *p*-aminobenzoic acid is not. Methylglucuronide, phenylglucuronide and probably resorcinyglucuronide are excreted by the tubules. Glucuronic acid itself and probably pregnanediol-glucuronide are not excreted in this way.

Hippuric acid, when given intravenously in relatively large quantities (100–200 mg.), depresses the excretion of all the above-mentioned substances which are excreted by the tubules.

The amide of *N*-methylnicotinic acid is also excreted by the tubules in the chicken. Apart from the very weak base, creatinine, this is the first instance known of the tubular excretion of a cation.

As seen from the above, products of most of the more important 'detoxication' mechanisms have been shown to be excreted by the tubules. The behaviour of 'ethereal sulfates' is at present under investigation. It would seem that the tubular excretion must be of considerable importance for the excretion of several normal constituents of the urine. The entry of 'detoxication products' into the urine is thus seen to be determined by the mechanism of their actual excretion as well as by the pathways of intermediary metabolism that lead to their formation.

STÄMPFLI, ROBERT (Bern). The action potential of the single myelinated nerve fiber.

Living single myelinated nerve fibers of frogs, toads, and pikes can be obtained by microdissection with fine steel needles under a binocular microscope. Their action potentials can be observed in a very satisfactory way by using the bridge method. The two nodes of Ranvier, including one internodal segment, are forming functional subdivisions of the nerve fiber, which we call *internodia*. The bridge

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method consists in placing each of the two nodes in separated electrode cups, filled with Ringer solution, while part of the internodal segment forms a bridge over an air gap of about $\frac{1}{2}$ –1 mm. Each cup contains a number of mutually insulated platinum wires perpendicular to the axis of the fiber. The whole arrangement is fixed into an electrically shielded moist chamber, thus permitting one to tap the action potentials at any desired point of the fiber. The internodal segment in the air gap dries out and has thus a high resistance of 20 to 50 megohms. The preparation is now put into one branch of a bridge circuit, balanced against a suitable impedance with a DC-amplifier as zero-indicator. The bridge AC-current of 50 cycles, used simultaneously as exciting and measuring current does not interfere with the action potentials formed, if the bridge is balanced. As in the internodal segment in air a block develops within several minutes, the observed action potentials are mostly monophasic. A displacement of the Ranvier node lying next to the air gap into the air gap leads to a rapid decrease of amplitude and increased duration of the potential. The all-or-none mechanism is lost and after a few minutes at most, the potential disappears completely. By crushing the fiber or by displacing the electrodes it can be demonstrated that an all-or-none response of the myelinated nerve fiber occurs only if an intact internodal segment with the two Ranvier nodes belonging to it (*internodium*!) is between the stimulating electrodes. As soon as only one node of Ranvier is lying between the electrodes, the all-or-none mechanism is lost. An internodal segment alone, without nodes, never gives more than polarisation notches, growing continuously with the exciting current. Very often, especially with old or stressed fibers, local responses can be seen, preceding the all-or-none type of propagated action potential in accordance to the local response observed by Hodgkin¹ on crustacean nerves. For the formation of a normal propagated impulse the interaction of two nodes of Ranvier and their internodal segment is necessary. Erlanger's² and von Murali's³ suggestion of discontinuous propagation from node to node and the supposition of the internodal segment acting as a separate unit thus receives strong support.

¹ Hodgkin, A. L., *J. Physiol.* 91, 5 P (1937). ² Erlanger, J., and Gasser, H. S., *Electrical signs of nervous activity*, Philadelphia, 1937. ³ von Murali, A., *Die Signalübermittlung im Nerven*, Basel, 1946.

STEN-KNUDSEN, OVE (Copenhagen). Investigations on the torsional elasticity on isolated frog muscle-fibers.

In anisotropic bodies there is no simple relation between Young's modulus, Poisson's ratio and the torsional rigidity which exists in isotropic media. An attempt is therefore made to investigate the torsional elasticity on isolated frog muscle-fibers and small fiber bundles to provide further information concerning intermolecular forces acting in the transverse direction of the fiber.

An isolated muscle-fiber or a thin bundle consisting of 4-5 fibers is fixed by its tendon end to a torsion wire (diameter 40 microns) with a known directional couple. The other tendon end is held by a pair of micro-tweezers which performs periodical angular movements the amplitude of which increases continuously from 0.38-2.50 radians with different frequency of 1-20 cycles per second. During the experiment the fiber is immersed in a bath of Ringer's fluid at different constant temperatures. When the fiber is twisted the movements of the torsion wire are recorded optically. From the known twisting angle of the fiber and the torsion angle produced in the wire the couple acting on the muscle-fiber can be determined. The longitudinal stretch is measured simultaneously by means of a condensor myograph (Buchthal). From the total couple as function of the torsion angle during rest and contraction under variable strain and constant temperatures the following facts can be deduced:

1. There is a linear correlation between the torsional deformation and the corresponding couple, i.e. the directional couple of the muscle fiber is constant at the torsion angles examined.
2. The directional couple shows an exponential increase plotted against the longitudinal strain.
3. The directional couple is 50-100 % higher during contraction than at rest.
4. In the frequency range investigated the magnitude of the directional couple is independent of the frequency.
5. The directional couple decreases with increasing temperatures.

The resulting torsional stiffness measured in a fiber under longitudinal stresses is determined by the torsional rigidity proper and a component due to a twisting of linear elements which in the untwisted state are in parallel with the rotating axis. The fact may be taken

in account in the following way: A mathematical analysis on the torque-twist curves obtained with various extensions will make it possible to find the distribution of the normal stress and the shearing stress over the cross-section of the fiber. From this distribution the torsional rigidity of the different fiber elements can be determined.

VALETTE, G., et CAVIER, R. (Paris). L'Activité des hormones sexuelles et corticales par voie transcutanée chez le rat.

La pénétration des médicaments par la peau est conditionnée par la nature du véhicule utilisé. En ce qui concerne les hormones œstrogènes on sait qu'une solution alcoolique de folliculine appliquée sur la peau est beaucoup plus active qu'une solution huileuse utilisée dans les mêmes conditions (Zondek).

Des essais systématiques entrepris, à la suite de Macht, sur les essences végétales et leurs constituants nous ont montré que l'eucalyptol est doué d'un grand pouvoir de pénétration à travers l'épiderme et nous ont incités à employer ce liquide pour réaliser l'introduction par la voie transcutanée des hormones sexuelles et corticales. L'eucalyptol présente en outre l'avantage d'être peu irritant pour l'épiderme contrairement aux solvants volatils habituellement préconisés.

Il résulte de nos expériences faites avec l'œstradiol que l'application de solutions de cette hormone dans l'eucalyptol sur la peau de rates ovariectomisées fournit des résultats 3 à 4 fois supérieurs à ceux que l'on obtient par injection sous-cutanée d'une solution huileuse ou par application cutanée d'une solution alcoolique; de plus, la durée de l'œstrus se trouve prolongée.

L'action de la testostérone a été étudiée chez le rat castré par l'appréciation de l'augmentation de poids des vésicules séminales et de la prostate. L'application cutanée de l'hormone mâle en solution dans l'eucalyptol provoque, du point de vue de l'intensité et de la durée, un effet analogue à celui que détermine l'injection sous-cutanée d'une solution huileuse de cette hormone et nettement supérieur à celui d'une solution alcoolique appliquée sur la peau.

L'étude de la capacité de travail musculaire chez le rat sur-rénalectomisé a permis de suivre l'administration de la désoxycorticostérone réalisée dans les mêmes conditions. Là encore,

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l'administration d'une même dose d'hormone, soit par voie sous-cutanée en solution huileuse, soit par voie transcutanée en solution dans l'eucalyptol provoque une restauration de l'ergogramme au bout du même nombre de jours, l'amplitude des contractions musculaires atteignant et dépassant la valeur initiale.

Il résulte de l'ensemble de nos expériences que, grâce à l'emploi d'un véhicule convenablement choisi, il est possible d'obtenir par l'administration transcutanée des hormones liposolubles un effet physiologique d'intensité sensiblement égale à celui que l'on réalise habituellement par injection hypodermique.

WALAAS, OTTO (Oslo). The effect of the estrogenic hormones on the glycogen content in uterus and liver.

The effect of the estrogens on the glycogen content in uterus and liver is studied in albino rats. The estrogenic hormones are found to induce an accumulation of glycogen in the uterus. Further a much greater increase in the glycogen content is observed in the muscularis than in the mucosa. The problem has been studied in adult rats during the sex cycle and in adult ovariectomized animals after injection of estradiolbenzoate, estrone and dioxydiethylstilbestrol.

The liver glycogen shows no alteration during the sex cycle. The liver glycogen content is neither affected by ovariectomy nor by injection of one single dose of estrogenic hormone. On the contrary, continued injections of estrogens in ovariectomized fasted rats increase the liver glycogen.

Further it is shown that in adrenalectomized animals also the estrogens will increase the glycogen content of the uterus. The estrogenic hormones therefore seem to have a direct increasing effect on the uterus glycogen.

WALSH, E. G. (Oxford). Electric threshold of human eye during dark and light adaptation.

Whilst the properties of the rods are commonly believed to change continuously and smoothly during dark adaptation, measurements of the electric threshold of the retina show discontinuities.

Pulses of exponentially decaying current (time constants between

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0.6 and 50 msec.) were applied across electrodes on the arm and cocaineized conjunctiva or forehead; threshold was taken as the strength which just elicited a white peripheral flash. At the start of an experiment the threshold was determined with the eye exposed to light reflected from a hemicylinder of white cardboard of radius 1 foot illuminated to 700 FC. The changes which occurred when the subject was plunged into total darkness may be divided into three phases:

Phase A occupied the first 20 sec. after the withdrawal of light; the threshold fell to $46 \pm 10\%$ of the initial value. This phase still occurred if the pupil was fixed with eserine or atropine.

Phase B occupied the ensuing 6–11 min., and the threshold was constant throughout. If however the initial adapting intensity was only 70 FC., or if the pupil had been constricted with eserine this phase did not appear and phase C followed directly on phase A; biphasic curves of this nature have already been published.¹

Phase C lasted about 10 minutes; the threshold climbed to reach a plateau at 80% of the initial value but determinations became progressively more difficult.

If the eye was re-exposed to light towards the end of phase B or during phase C the threshold (I) rose very rapidly to a high value (e.g. 300% initial) and (II) fell in 3–6 min. to a value close to that at the start of the experiment; the apparent brightness of the background and the threshold seemed to run parallel.

The retinal structures stimulated by these pulses are probably the rods themselves; cones do not seem to be implicated as their dark adaptation is complete in about 3 min., moreover the slow rise of threshold in the dark still occurs after preadaptation to light too weak to stimulate cones.¹ The delayed appearance of this slow rise after preadaptation to bright light suggests that in these experiments the rods are indifferent to photochemical regeneration until a critical level is reached. The experiments were performed in collaboration with Miss P. Frodsham.

¹ Barlow, H. B., Kohn, H. J., and Walsh, E. G., *Amer. Journ. Physiol.* 148, 376 (1947).

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WATERS, E. T., GORANSON, E. S., and BALASUBRAMANYAM, G. (Toronto). **Insulin in blood.**

It has been shown that when paired leg muscles (chiefly sartorii) of frogs have been immersed in frogs' Ringer's solution, containing radioactive phosphorus (P^{32}), at 5° C. for 12 to 16 hours the 'turnover of phosphocreatine' (the counts on the Geiger-Muller counter per minute per milligram of phosphocreatine phosphorus, isolated) is greater in the muscle immersed in Ringer's solution to which a minute amount of insulin has been added. There is a rough proportionality between the difference in turnover values and the amount of insulin added, when the insulin has been added in amounts of from about 1/1000 to 1/100 unit per c.c. of Ringer's solution. It is suggested that this sensitive test may prove to be a useful method for the approximate estimation of minute amounts of insulin. The method has been applied to the detection of changes in the insulin of dog blood, by immersing the paired muscles in the plasmas to be compared.

WHITTERIDGE, D. (Oxford). **Afferent impulses from the heart and lungs.**

In the cervical vagus the most conspicuous afferent fibres detectable by electrical methods are, of course, the pulmonary stretch fibres and the aorta depressor fibres (*Adrian*, 1933). In addition, there are at least three other types of fibre which appear to arise from the heart and lungs. Fibres which have *a c* and *v* volleys corresponding to the *a c* and *v* waves of the auricular pressure pulse are common. The majority can be shown to follow the effective pressure in the venae cavae faithfully. The remainder behave as if their endings lay on the roots of the pulmonary veins. Similar impulses from venous receptors were reported by *Amann* and *Schaeffer* (1943).

A second group show a systolic rhythm later in onset than the arterial pressure wave, and varying quite independently of the systemic arterial pressure. Their activity is greatly increased by an increase in venous returns and by intrathoracic negative pressure, and they appear to arise from arterioles or capillaries in the lung. The duration of their impulses is nearly twice as long as that of

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stretch fibres, and unlike all other fibres so far seen, they survive cooling to between 4–8° C. It is possible that they play a part in the production of deflation reflexes.

A third group show a very early systolic discharge, corresponding to the isometric contraction phase. They have been seen to be active after an extrasystole which failed to open the aortic valves. They increased greatly in activity during positive pressure inflation of the lungs, which lowers the aorta pressure, but is believed to raise the right ventricular pressure. Their endings appear to be related to the ventricular wall.

Adrian, E. D., *J. Physiol.* **79**, 332 (1933).
Pflüg. Arch. ges. Physiol. **246**, 757 (1943).

Amann, A., and Schaefer, H.

YOUNG, E. G., and PHINNEY, J. I. (Halifax, Canada). **The proteins of egg yolk of the atlantic salmon.**

The proteins in the yolk of the unfertilized eggs of the Atlantic salmon (*Salmo salar*) have been fractionated by several methods. The yolks were diluted with 10% sodium chloride or 2% ammonium sulphate and exhaustively extracted with diethyl ether. A lipoprotein was precipitated from the resulting aqueous solution at its iso-electric point of pH 3.7. It contained about 3% lipid, extractable by treatment with ethanol at 7% concentration. It appeared to be readily denatured and could be redissolved only partially in dilute ammonia at pH 8. On analysis it exhibited a concentration of N—15.73% and P—1.32% on a moisture-free and ash-free basis. Only a trace of an albumin-like protein remained unprecipitated.

The lipoprotein was also isolated by the Piettre technique with acetone at a concentration of 70%.

The proteins of the yolk have also been analysed by electrophoresis.

GERNANDT, B., and ZOTTERMAN, Y. (Stockholm). **The splanchnic efferent outflow of impulses in the light of ergotamine action.**

For an analysis of the action of ergotamine upon the arterial blood pressure of the cat the action potentials were recorded from efferent fibres of the splanchnic nerve.

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When ergotamine is given in a moderate dose of 0.05 mg. per kg. body-weight, asphyxiation or the inhalation of air rich in carbon dioxide was found to produce a fall instead of the usual rise in blood pressure. The electric response, however, differs only in that the response now starts earlier and is more accentuated.

After a pithing of the brain and the medulla oblongata the efferent outflow in the splanchnic nerve reacts to asphyxiation and carbon dioxide in a way very similar to the reaction in the intact cat, but the response is more rapid and more pronounced than in the intact animal. Ergotamine does not produce any change whatever in the splanchnic efferent outflow in the spinal cat.

This shows that inhibitory influences upon the spinal vasomotor centres are exerted from higher centres, which influence is abolished by ergotamine even in moderate doses, as has been shown by *Rothlin, Wright and Euler*, and *Schmürlöw*.

When giving increasing doses of ergotamine it was found that the effect of faradic stimulation of the peripheral end of the splanchnic nerve, which normally causes a rapid rise in the blood pressure, became more and more delayed and depressed, until after large doses the effect was reversed. At this stage the adrenaline effect was also reversed. Even as small doses of ergotamine as 0.05 mg. per kg. body-weight exert a distinct peripheral action. The reversed effect of asphyxia thus seems to be due to the fact that the peripheral dilatory action of CO_2 is no longer sufficiently counteracted by the efferent sympathetic outflow as the peripheral effect of these impulses is weakened or abolished by ergotamine.

The recording of the action potentials from the splanchnic nerve did not yield any proof of any activity of specific vasodilatory fibres either before or after ergotamine.

ASTRUP, TAGE (Copenhagen). Fractionation of proteins by means of protein precipitating agents.

It has been known for some time that substances commonly used for removing proteins from fluids, such as trichloroacetic acid, metaphosphoric acid, &c., under certain conditions are able to combine with and precipitate proteins without denaturation and other irreversible changes. Thus *Kunitz* and *Northrop*¹ showed that

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trypsin could be precipitated by means of 5% trichloroacetic acid and afterwards be regained without loss of activity. *Perlmann* and *Herrmann*² precipitated egg albumin with metaphosphoric acid and were able to regain crystalline egg albumin from the precipitate. *Perlmann*³ further prepared a crystallized egg albumin metaphosphate. *Anson*⁴ purified cathepsin by means of a precipitation with tungstic acid. Spread in the literature we were able to find other examples of the purification of proteins by means of protein precipitating agents.

These observations suggested to us that this method of precipitating and purifying proteins might be of general applicability and in collaboration with *Aksel Birch-Andersen* experiments were undertaken in order to disclose this question.

It is known, cf. *Dexter, Haynes, and Bridges*,⁵ that renin may be purified by means of trichloroacetic acid, which at pH 2.9 precipitates impurities. We have succeeded in finding a method for fractional precipitation, using sulphosalicylic acid and tungstic acid, by means of which purified, potent renin preparations may be obtained in a very simple manner. We have further investigated the action of the precipitating agents on serum proteins, using electrophoresis after *Tiselius*, in order to study the different actions of the various agents on a protein mixture, the properties of which are comparatively well known. We have found that it is possible, when using various agents and by changing the conditions, to obtain a high degree of selectivity in the precipitations, and we are therefore of the opinion that we have here a new general method for the fractional precipitation of proteins.

¹ Kunitz and Northrop, *J. Gen. Physiol.* 19, 991 (1936). ² Perlmann and Herrmann, *Biochem. Jour.* 32, 926 (1938). ³ Perlmann, *Biochem. Jour.* 32, 931 (1938). ⁴ Anson, *J. Gen. Physiol.* 23, 695 (1940). ⁵ Dexter, Haynes, and Bridges, *J. Clin. Inv.* 24, 62 (1945).

BARGETON, DANIEL (Paris). Contribution à l'étude du rôle physiologique des sels biliaires. Étude quantitative de leur action cholérétique.

Les sels biliaires sont les corps les plus cholérétiques que l'on connaisse. Éliminés électivement par le foie et réabsorbés dans l'intestin, ils peuvent être considérés comme excitant physiologique de la

sécrétion biliaire. Leur action cholérétique a été étudiée sur le lapin à jeun après injection intraveineuse, le débit biliaire étant enregistré de façon continue pendant plusieurs heures. L'élément le plus constant de la réponse cholérétique provoquée par des doses égales d'un même sel biliaire est l'accroissement maximum du débit de bile survenant dans les minutes qui suivent l'injection. Entre cet accroissement

S et la dose D il existe une relation simple $S = k \log \left(1 + \frac{D}{d}\right)$

dans laquelle k et d sont deux constantes. On peut proposer pour d une signification physiologique si l'on admet que le sel biliaire injecté est d'emblée fixé électivement sur le foie et que sa concentration y passe de la valeur c à la valeur C ; m étant la masse du foie, la relation devient $S = k \log \left(1 + \frac{D}{mc}\right)$ ou $S = k \log \frac{C}{c}$ exprimant que

l'accroissement maximum du débit de bile est proportionnel au logarithme de la concentration C du sel biliaire dans le foie si l'on prend pour unité sa concentration initiale c . L'expérience donne pour $d = mc$ des valeurs compatibles avec les données admises pour la masse du foie et sa teneur en sels biliaires. La constante k caractérise l'activité du sel biliaire. La relation trouvée se vérifie avec une approximation de l'ordre de grandeur des erreurs de mesure entre les doses de 2 à 100 et 200 mg./Kg. pour 7 sels biliaires essayés, la bile cristallisée de Plattner et la bile fraîche de lapin.

Si l'on injecte à un même lapin deux sels biliaires différents les résultats observés s'expriment d'une façon satisfaisante en donnant à la constante $d = mc$ la même valeur qui semble donc bien dépendre de l'animal et en donnant à k deux valeurs qui expriment le rapport des activités cholérétiques des sels essayés. On en déduit que le rapport entre les réponses cholérétiques à deux doses égales de deux sels biliaires différents est indépendant de la dose, ce que vérifie l'expérience.

La forme de la relation existant entre la réponse cholérétique et la dose de sel biliaire qui la provoque conduit à penser que des processus physiques plutôt que des processus chimiques interviennent dans l'action excitante des sels biliaires sur l'excrétion de la bile.

BROWNE, J. S. L., SCHENKER, V., and JOHNSON, L. G.
(Montreal). **Certain aspects of protein metabolism and
nutrition in patients with chronic diseases.**

The metabolic investigations conducted in this laboratory during the past five years have demonstrated that, in adult patients acutely injured (burns, fractures, &c.) whilst in good health, the nitrogen metabolism undergoes certain changes which follow a characteristic pattern starting at the time of injury, and lasting through convalescence to subsequent recovery of health. This phenomenon, apparently independent of the type of trauma sustained, has been termed the 'Nitrogen Catabolic Response'. The pattern consists essentially of a markedly increased rate of excretion of nitrogen in the urine which reaches a maximum within the first week or ten days after injury, then subsequently merges into a second period during which the nitrogen excretion rate becomes considerably lower, even when compared to healthy control subjects on the same food intake. The mechanisms responsible for these changes are not known.

In the course of these studies it was observed that this metabolic pattern was not manifest in patients debilitated by chronic disease. Investigations were therefore instituted to gain more knowledge regarding the reasons for this difference and in the hope of throwing more light on the mechanism(s) controlling the 'Catabolic Response' phenomenon.

The present communication deals with the findings of these studies.

A series of hospital patients chronically ill with diseases such as rheumatoid arthritis, bronchiectasis, pulmonary tuberculosis, peptic ulcers, were studied under controlled intakes of food at various levels and for definite periods of time. Nitrogen balance, nutritional status, body-weight, and general clinical course were carefully followed.

It was found that, in contrast to the acutely 'damaged' individuals mentioned above, these 'metabolically debilitated' subjects displayed a remarkable ability to retain their food-nitrogen at comparatively low dietary intakes, which, when raised to higher levels, led to more marked positive nitrogen balance and weight gain. In general, a noticeable clinical improvement was apparent concomitant with the improved nutritional status. This was so particularly in the case of

the patients with peptic ulcer, bronchiectasis, and rheumatoid arthritis. However, in those patients with pulmonary tuberculosis, little or no roentgenological evidence of healing could be demonstrated in spite of their increased vigour, feeling of well-being, and gain in body-weight. It thus appears that the 'debility' of chronically ill patients, which is so commonly attributed to the 'toxic effects' of some specific disease, may largely be due to under-nutrition.

The foregoing experimental data are discussed as to the possible mechanisms involved in producing these abnormalities in metabolic behaviour.

CORDIER, D., et CORDIER, G. (Lyon). Influence des réflexes respiratoires d'origine aortique et sino-carotidienne sur la résistance à l'anoxie et à l'asphyxie progressives.

L'étude a été faite sur des chiens anesthésiés au chloralose.

1. Anoxie progressive

(a) Les chiens vagotomisés augmentent progressivement leur ventilation à mesure que le taux d'oxygène diminue. Ils succombent, comme les animaux témoins, pour un taux d'oxygène dans l'air inspiré variant de 2,5 à 3,5 % après avoir présenté une hyperventilation comparable. La vagotomie ne diminue pas la résistance à l'anoxie progressive.

(b) Les chiens à sinus carotidiens extirpés augmentent progressivement leur ventilation à mesure que le taux d'oxygène diminue. L'augmentation est comparable à celle des animaux témoins jusqu'à 13 % d'oxygène environ. Puis, l'hyperventilation reste inférieure à celle des animaux témoins et les concentrations mortelles d'oxygène varient entre 3,50 et 8,0 %. L'extirpation des sinus diminue la résistance à l'anoxie progressive. La seule ligature des carotides primitives ne modifie pas la résistance à l'anoxie; la modification de l'irrigation des centres n'est donc pas responsable du phénomène.

(c) Les animaux vagotomisés et à sinus extirpés ont une résistance très variable. Les concentrations mortelles d'oxygène varient de 3,5 à 11 %. Le centre respiratoire privé des chémoréflexes régulateurs répond à l'anoxie progressive d'une manière assez désordonnée. Un type de respiration périodique s'établit souvent à partir de 13 % d'oxygène. L'extirpation supplémentaire des ganglions étoilés et

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cervicaux supérieurs ne change pas le comportement des animaux de ce groupe.

La sensibilité *directe* du centre respiratoire à l'anoxie progressive est donc très nette chez les chiens anesthésiés au chloralose.

2. *Asphyxie progressive*

Les animaux vagotomisés et les animaux à sinus carotidiens extirpés succombent, comme les animaux normaux, pour une teneur en oxygène voisine de 3 %.

Les animaux vagotomisés et à sinus extirpés ont une résistance très peu diminuée. Les concentrations mortelles d'oxygène varient entre 3,7 et 6,3 %. L'hyperventilation est comparable à celle des animaux témoins. Au cours de l'asphyxie progressive il y a donc prédominance de la régulation centrale sur la régulation réflexe. Chez les chiens privés de leurs chémorécepteurs réflexogènes, l'acide carbonique a une influence régulatrice sur la réaction du centre respiratoire souffrant d'anoxie.

EMERSON, G. A., WOOD, T. R., and HOWE, E. E. (Rahway, N.J., U.S.A.). **Nutrition studies with diets containing varying sources of amino acid nitrogen.**

Weanling male rats were fed purified diets of equal nitrogen content but containing varying sources of amino acids. All identified vitamins were supplied in the rations. The order of growth response (greatest to least) for a 28-day test period was: (1) casein; (2) trypsin digest of casein; (3) acid digest of casein plus tryptophane; (4) mixtures of amino acids. The food consumption, in general, paralleled the weight increments. Replacement of the amino acid mixtures or the acid digest by casein to the extent of 5, 10, or 15% of the ration resulted in increased growth. However, weight gains and food intakes comparable with those of the controls were seen only in those animals receiving the 15% level of casein. Possibly the poor response obtained with mixtures of amino acids was ascribable in part to palatability. The better growth observed with the trypsin hydrolysate and with casein as contrasted with the acid digest may indicate the need on the part of the rat for an unidentified factor(s).

Reproductive performance was studied in rats of both sexes main-

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tained on the amino acid or casein containing diets. First generation males receiving the amino acid mixtures bred normally. The young of females fed this same ration were undersized at weaning. The average weight was 24 gm. as contrasted with 34 gm. for the young of females fed the casein-containing diet. The young of the latter group compared favorably with those weaned from mothers maintained on purified diets containing liver or with those given a natural food ration. The difference in growth was even more striking at 3 months at which time the average weights were 157 gm. (amino acid mixture) and 366 gm. (casein).

GUTTMANN, L. (Stoke Mandeville). **Disturbances of autonomic mechanisms after spinal cord injuries in man.**

The first part of this communication deals with the disturbances of sudomotor function as revealed by the thermoregulatory sweat test in over 50 cases with spinal cord injuries. The quinizarin-method (Guttmann, 1937, 1941, 1947) was used as an indicator of sweat gland activity. In cervical injuries special attention was paid to the sweat disturbances in incomplete lesions. Two kinds of disturbance were found: (a) unilateral, involving the whole of one side of the body, (b) segmental, affecting certain dermatomes of the body only. The sweat disturbance demonstrates only the distribution of sudomotor fibres and is dissociated from the disturbance of motor and sensory functions. Frequently dissociations between sudomotor and oculo-pupillary function were also found, indicating a separate location or different vulnerability of fibres subserving these two autonomic functions. In lesions of the thoracic cord the problems of the topographical relations of spinal segments to sudomotor function in comparison with sensory function are discussed. In cauda equina lesions the thermoregulatory sweat test proved invaluable for distinguishing two groups of lesions: those uncomplicated and those complicated by superimposed lesions of peripheral nerves and sympathetic trunks or ganglia.

The second part of the paper deals with the effects of bladder distension on sweating and cardiovascular mechanisms after spinal cord injuries. This study was carried out in co-operation with D. Whitteridge. Bladder distension in complete lesions above Th. 12

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sets up reflex responses of autonomic mechanisms which are dependent in constancy and intensity on the level of the lesion. They were most conspicuous in all cases with lesions at or above Th. 5. In these cases the skin temperature rose in the neck and face while there was a drop of skin temperature of the feet, with rectal temperature showing only a slight rise. There was a very large rise in the systolic and diastolic blood pressure. During the period of raised blood pressure a steep fall in pulse volume and blood flow in fingers and toes occurred. Sweating was profuse in face, upper limbs, and upper chest and to a much less degree down to Th. 10. The pulse rate showed a marked drop, there were extrasystoles and occasional bigeminy and the electrocardiogram revealed large U-waves. In contrast to these cases lesions between Th. 6 to Th. 10 showed only slight changes of blood pressure and in more distal lesions no blood pressure changes were found. These cases showed evidence of vasoconstriction in feet and legs only whereas the fingers and upper parts of the body showed definite signs of vasodilatation. The mechanism of this mass response of autonomic functions due to bladder distension is discussed.

HAIG, C., and HAIG, E. M. (New York). **Retinal sensitivity contours.**

The sensitivity (reciprocal of minimal perceptible brightness) of the retina to violet and to red light has been measured in the horizontal meridian at zero degrees, at 2, 4, 6, 8, 10, 15, 20 degrees temporally, and at 2, 4, 6, 8, 10, 20 degrees nasally to the fovea. For measuring rod sensitivity the eye was completely dark-adapted and the test stimulus was violet light ($< 460 \text{ m}\mu$) to which the rods are maximally sensitive. For measuring cone sensitivity, the eye was first exposed for 3 minutes to a white light (2360° K) having a brightness of 1700 millilamberts. The threshold brightness for red light ($> 680 \text{ m}\mu$) was then determined after 5 to 7 minutes of darkness, at which period the cones are completely dark-adapted while the rods are still non-functional. Using red light for cone measurements differentiates with greater certainty cone (red) and rod (white) responses.

The Hecht-Shlaer dark adaptometer was used, in which the bright-

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ness is controlled by neutral filters and a photometric wedge. The circular test image subtended one degree of visual angle and was flashed on for 0.2 second by means of a calibrated camera shutter. The location of the image on the retina was controlled by allowing the subject to fixate on a very small, dim light placed at various angles to the center of the test field. Sensitivity is expressed as log reciprocal of the threshold brightness in lamberts.

The sensitivity to violet light of the dark-adapted rods increases about one log unit from 2 degrees out to 10 degrees. The function remains constant out to 20 degrees temporally, but falls by about 0.2 log unit at 20 degrees nasally.

At zero degrees the measurements are necessarily those of pure cone function, as the one degree test image falls within the 1.5 degree rod-free area of the fovea centralis. The central cones are histologically different from the peripheral cones. Their sensitivity is about 2 log units lower than that of dark-adapted rods to violet light at 2 degrees, while the larger cones at 2 degrees have a sensitivity about 0.25 log unit higher than that of the thinner central cones. From this point outward the sensitivity steadily decreases to 20 degrees where it is about one log unit lower than at 2 degrees.

HELLER, H. (Bristol). **Posterior pituitary control of neonatal water metabolism.**

The very low content of antidiuretic hormone of new-born rat pituitary glands (Heller, 1947), together with the morphological evidence for the immaturity of the mammalian neurohypophysis at birth, suggested the possibility of neurohypophysial hypofunction in the new-born. If such a hypofunction exists, new-born animals should show a feature which is prominent in cases of clinical and experimental diabetes insipidus: they should, even under stress, be unable to concentrate the urine to the same degree as adults. New-born rats, kept at 30–31° C., were deprived of fluid for 24 hours and the concentration of their urine was compared with that of the urine of adults which had been deprived of water for the same period. Estimations of the specific gravity, of the freezing point depression, and of the main osmotically active constituents showed that the new-born animals failed to concentrate the urine to any considerable

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degree. Does the absence of the adult type of response to water deprivation impair the physiological efficiency of the new-born animals? It could be shown that it does, in so far as, in contrast to adults under comparable conditions of stress, new-born animals were unable to maintain an unchanged internal environment: the extrarenal water loss in the adult and the new-born series was statistically the same but the volume of urine excreted during the 24 hours of withdrawal of fluid (though low in both series) was significantly higher in the new-born animals. This finding agreed with the results of determinations of the water content of blood and muscle samples. Significant decreases were found in those of the new-born animals while their more economically functioning kidney enabled the adult rats to maintain the water content of these tissues unchanged. Plasma water losses of a magnitude similar to that suffered by new-born animals after 24 hours were observed in adult rats after several days of dehydration only, indicating again that the state of 'physiological diabetes insipidus' was a significant factor in the liability of the new-born animals to dehydration.

HITCHCOCK, F. A., EDELMANN, A., and WHITEHORN, W. V.
(Columbus, Ohio). **Physiological responses to explosive decompression.**

It has previously been reported from this laboratory that animals tolerate explosive decompressions over ranges as great as 8,000 feet to 50,000 feet in as short a time as 0.02 second. Physiological responses observed included expansion of the thorax and abdomen, slowing of the heart, a drop in arterial blood pressure, and an increase in intrathoracic and cerebrospinal fluid pressures. We believe that these responses, except the distention of the abdomen, are the result of an increase in intrathoracic pressure.

With human subjects, experiments have demonstrated that explosive decompressions to altitudes as high as 40,000 feet in 0.1 second are without harmful effects. A series of experiments are now under way designed to determine the physiological effects of explosive decompression to altitudes between 70,000 and 80,000 feet. At these pressures body fluids should boil at body temperature. Rats and dogs have been used in such experiments. The outstanding effect

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with both species is a swelling of the body which begins between ten and thirty seconds after the explosive decompression. The swelling is apparently due to the rapid vaporization of body fluids and appears to occur in subcutaneous tissues. When the pressure is increased to a value of approximately 50 mm. Hg., this swelling diminishes.

A technique has been devised for measuring the effects of explosive decompressions to such high altitudes on the volume of the lungs. Results obtained with this technique indicate that daily explosive decompressions for at least five days are necessary to produce significant atelectasis.

If experimental dogs are brought down to a simulated altitude of about 40,000 feet (141 mm. Hg.) within two minutes of the time the explosion occurs, the majority of the animals survive. However, exposure to 30 mm. Hg. for three minutes is almost universally fatal. Rats rarely survive exposures to 30 mm. Hg. of more than 100 seconds, and after return to ground level, usually show a profuse pulmonary exudate, which is probably due to an increased permeability of pulmonary capillaries. Investigations are in progress to determine the effects of various procedures on capillary permeability and fragility. Studies are also being carried out on the circulatory responses and on the changes in thoracic, abdominal, subcutaneous, and cerebrospinal fluid pressures resulting from explosive decompression to 30 mm. Hg. Possible temperature changes in the lungs are being investigated. In this work we are endeavouring to distinguish between the effects of explosive decompression per se and the effects of anoxia.

JIMENEZ-VARGAS, JUAN (Barcelona). The innervation of the external sphincter of the urethra.

An experimental study of the facts observed by means of the stimulation of the distal end of the cut internal pudic nerve is carried out and the electric and contractile responses of the bulbo-cavernosus muscle and of the external sphincter are compared.

A similar study has been accomplished with the stimulation of the nervus erigens.

The contractile response of the bulbo-cavernosus muscle to the

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stimulation of the internal pudic nerve is always very well manifested, by contrast with the uncertainty of the response of the external sphincter muscle.

The stimulation of the *nervi erigentes* does not produce an appreciable response of the bulbo-cavernosus, but instead a contractile response of the external sphincter muscle is observed.

Without the accomplishment of definitive conclusions, the interpretation of all these experimental facts suggests that possibly the innervation of the external sphincter by the internal pudic nerve is not fundamental for the function of the external sphincter.

KLEYNTJENS, F. (Brussels). **Observations on the central mechanism of fever.**

Fever has been induced in rabbits either by intravenous injection of typhoid vaccine or by hypothalamic puncture. The symptoms accompanying hyperthermia are identical in both cases: intense vasoconstriction of the ears, slow respiration, increased muscle tone and more or less obvious shivering. The threshold of thermal polypnea is definitely raised as shown by experiments in a hot box.

The syndrome is essentially of an excitatory nature as shown by experiments of injection of depressing drugs (by a very thin needle) into the hypothalamic structures: traces of calcium chloride or urethane provoke at once maximal vasodilatation and suppression of shivering, soon followed by a fall of rectal temperature. Contrasting with these symptoms of defervescence, an additional and paradoxical rise of threshold of thermal polypnea is observed.

The effects of thermal puncture may be divided into immediate, unspecific ones (e.g. possibility of initial vasodilatation) due to mechanical stimulation of hypothalamic neurones, and delayed, specific ones presumably related to the diffusion and pharmacological action on the thermoregulatory structures of substances released by the local trauma.

The direct pyrogenic effect of substances has been verified by the method of their hypothalamic injection in normal rabbits (the traumatic effect being excluded by sufficient preliminary period of observation), and comparison of the minimal pyrogenic dose of the same substance when injected into other parts of the brain. These

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experiments have demonstrated a direct pyrogenic effect of bacterial toxins and of histamine. The specificity of their final effects was ascertained by the coordination of febrile symptoms and by the rise of threshold of thermal polypnea, which could be detected even when the hyperthermia was very slight.

These experiments contribute to demonstrate that in fever the functional disturbance of the thermoregulatory centre does not destroy the reciprocal innervation of its thermolytic and thermogenetic components.

LEÃO, A. A. P. (Rio de Janeiro). **Further observations on the spreading depression of activity in the cerebral cortex.**

A slow voltage variation, having a duration of 4 to 6 minutes, accompanies the *spreading depression of activity* in the rabbit's cerebral cortex. This response, elicited by local stimulation, has been described previously (*J. Neurophysiol.* 7, 359-90, 391-6, 1944; 8, 33-46, 1945). Each cortical region first becomes negative with respect to an extracortical reference electrode, for 1 to 2 minutes. This negativity reaches, within 0.5 to 1 minute, a maximum of 8 to 15 mV. and then decreases somewhat more rapidly. The region then becomes positive for 3 to 5 minutes, this phase having, as a rule, a smaller amplitude than the negative. As the region first becomes negative, its 'spontaneous' electrical activity begins to decrease and its pial arteries to dilate.

A sudden cortical anemia, resulting from a 1-minute arterial occlusion, abolishes the 'spontaneous' activity without itself inducing a slow voltage variation, but it promptly and profoundly alters the slow voltage variation accompanying the spreading depression of activity. This alteration, which outlasts (up to 2 minutes) the period of arterial occlusion, consists essentially of a prolongation and an increase of the negativity. If the period of anemia coincides with the decline of the negative phase or the initiation of the positive, the region returns to negativity, with a second negative peak appearing in the voltage curve.

In a cortex, in no part of which a spreading depression of activity is in progress at the time, interruption of the circulation for longer periods induces a slow voltage variation only 3 to 5 minutes after the

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arterial occlusion, at which time the cortex becomes negative. This negativity develops identically as when a cortical region is reached by a spreading depression of activity, and is of comparable voltage. The cortex then remains negative for as long as the circulation is interrupted (up to at least 12 minutes). If the prolonged anemia is started while a cortical region is involved in a spreading depression of activity and exhibiting the slow voltage variation, then the negativity, promptly induced in the region, persists for as long as the arteries are occluded (up to at least 12 minutes).

LUNDQUIST, FRANK (Copenhagen). **A method for estimating the relative amounts and chemical composition of the secretions constituting human semen.**

It has been known since the work of *Broesike* in 1911 that the secretions from the various accessory sex glands in man are not expelled simultaneously during ejaculation. Quantitative data as to the amount, composition, and the time course of evacuation of the individual secretions have so far not been available. Chemical studies on prostatic secretion and secretion from the seminal vesicles obtained through digital massage have been reported by several authors and the amount of prostatic secretion in semen has been evaluated by *Gutman* on the assumption that the first part of the ejaculate consists of pure prostatic secretion. Other studies have been made on fractionately collected semen, though only of a qualitative nature.

Making the following assumptions, quantitative data may, however, be obtained through determination of acid phosphatase, fructose, and the number of spermatozoa in each fraction.

1. The secretions from the prostate, the seminal vesicles, and the testis-epidymis do not alter their composition during ejaculation.
2. The secretion from Cowper's glands is evacuated before the ejaculation proper and even if this is not the case the amount of this secretion is negligible compared with the other components.
3. Acid phosphatase is present only in the prostatic fluid, fructose is present only in the secretion from the seminal vesicles, and spermatozoa are found only in the testis-epidymis secretion.

If ejaculate is collected in 3 or more fractions, 12 equations with

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12 unknown quantities may be formed. These equations are easily reduced to 3 containing as unknowns only the concentration of phosphatase in prostatic fluid, the concentration of fructose in seminal vesicle fluid and the number of spermatozoa in the testis-epididymis secretion. From these 3 values the other 9 quantities, viz. the amounts of each of the 3 secretions in each of the fractions may easily be calculated.

Experimental procedure. The experimental subject is instructed to collect the ejaculate fractionately in a special tray with six compartments.

After liquefaction the fractions are weighed and analyses performed, 0.05 ml. of each fraction is used for counting spermatozoa, 0.05 ml. is used for phosphatase determination and 0.1 ml. is used for fructose determination. Generally, there is ample fluid left for additional analyses making possible determinations of the concentration of other substances in the secretions constituting the ejaculate.

MACINTOSH, F. C., and PATON, W. D. M. (London). **The release of histamine by amidines and other compounds.**

The trypanocidal diamidines and certain other organic bases have a characteristic effect on the blood pressure of the cat. When one of these compounds is injected intravenously into a cat anaesthetized with chloralose, the blood pressure is not immediately affected, but suddenly falls after a delay of about 20 seconds. The following evidence indicates that the delayed depressor effect is due to the release of histamine. (a) Plasma taken from the cat after the blood pressure has fallen has an immediate depressor action when injected into another cat, and contracts an isolated strip of guinea-pig's ileum: the two tests agree as to the amount of histamine present in the plasma. (b) The effect of the post-injection plasma on both the blood pressure and the gut is not abolished by atropine, but is abolished by neoantergan in doses just sufficient to annul the effect of histamine. (c) The post-injection plasma retains its activity when deproteinized and heated with strong HCl, as in *Code's* method for estimating histamine in blood. (d) The slow intravenous injection of one of the compounds elicits a secretion of acid gastric juice in the anaesthetized cat. (e) Injection of dilute solutions of the compounds

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into human skin produces a typical 'triple response'. The main site of histamine liberation appears to be skeletal muscle. The most active compounds tested were stilbamidine and propamidine. Activity was also shown by straight-chain diamines, diamidines and diguanidines with the basic groups terminally placed, by some aromatic monoamidines, and by licheniformin, the antibiotic isolated by Callow and Hart from *B. licheniformis*.

MALMÉJAC, J. (Algiers). Les modifications protidiques sanguines en anoxie.

Cette étude expérimentale est réalisée sur des animaux divers, soumis au caisson à dépression à des anoxies d'intensité et de durée variables; certaines expériences durent 3 à 4 heures. Dans d'autres, les séances au caisson sont répétées journalièrement pendant plusieurs semaines.

L'étude des protéines sanguines est réalisée par méthode électrophorétique. Des prises de sang artériel sont faites avant et après l'épreuve au caisson, tous les 4 à 5 jours quand l'expérience est prolongée.

Les résultats montrent qu'il y a surtout des modifications touchant aux globulines β et γ , dont la cause est discutée. Les influences réciproques de la perméabilité capillaire et des modifications biochimiques sont envisagées.

MONCHE, J., JIMENEZ-VARGAS, J., and SOLS, A. (Barcelona). Distribution of phosphomonoesterases in the dog.

From five dogs the following isolated organs are removed separately: brains, parotids, thyroids, lungs, hearts, livers, spleens, stomachs, small and large intestines, pancreas, kidneys, suprarenals, a portion of skeletal muscle, testicles and prostates from the males; and ovaries and uterus from the females, and skeletal muscle.

After the estimation of the weight of all these organs they are fragmented and mixed separately in order to obtain a homogeneous part which is triturated with sand and autolysed by means of chloroform water 1/10(w/v) during twenty-four hours at the room temperature and with stirring from time to time. Then it is filtered through cotton and the resulting filtrates conserved in an ice-box until used.

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By the *Sols*'s method phosphomonoesterases are estimated quantitatively at pH 9.4, 5.0, 3.75, and 6.5 (A_1 , A_2 , A_3 , and A_4), after convenient dilution of extracts in order to bring them to an optimal concentration in connexion with the pH to be employed, which is evaluated by means of a previous computation.

Employing the same extracts, the influence of the following agents on the activity of phosphatases of each of all these above-mentioned organs is tested: CN on the A_1 ; alcohol treatment and fluoride treatment on the A_3 .

The corresponding results are contrasted and discussed comparatively with others of similar but pure isolated phosphatases, by means of *Albers*' technique.

MONNIER, A. M. (Paris). The role of calcium complexes in the elicitation of spontaneous rhythmical nervous activities.

Since the pioneer work of *Sydney Ringer*, calcium has been recognized as a fundamental constituent of body fluids. Absence of calcium leads to tetany, i.e. spontaneous activity of nerve cells. Rhythmical nervous activity can be elicited more readily by decalcifying salts. Among such salts sodium phosphates are the most interesting. They disclose the spontaneous rhythmical response of nervous tissue without exerting any toxic effect. For instance, adequate injection of sodium phosphate to a spinal frog produces a marked enhancement of reflex after discharge for several days. The same effect could not be obtained with another decalcifying salt, such as sodium citrate, as the toxic action exerted leads to cardiac arrest (*Bonnet* and *Monnier*). Moreover, sodium phosphates at high concentrations induce a long-lasting spontaneous and synchronized response of the isolated medullated nerve (*Monnier*).

The efficiency of sodium phosphates as decalcifying agents can be explained by the following arguments:

(a) A mixture of primary and secondary sodium phosphate is a buffer, the pH of which can be adjusted. Thus decalcification can be made to proceed at any required pH.

(b) Phosphate ions are normal constituents of tissues and body fluids. Consequently they are non-toxic and can be used at high concentration, thus exerting a marked decalcification without injury.

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The effect of decalcifying salts results from the formation of calcium complexes. Decalcification exerted by sodium phosphates results from the combination of calcium into complexes, with secondary phosphate ions. (Greenwald and Monnier.)

Complex formation with either calcium or magnesium is a general process. Such complex formation is obtained with all substances presenting several acid functions (i.e. organic diacids, amino-diacids and proteins). For instance if titration of a diacid is performed in presence of calcium chloride the following feature appears: the first part of the titration curve remains the same as in the absence of calcium, thus indicating that the neutralization of the second acid function proceeds without change. But the neutralization of the second acid function occurs at lower pH, as shown by the marked shift of the corresponding section of the titration curve. This shift results from the formation of a calcium complex at the expense of the secondary anions of the diacid and permits an accurate measurement of the dissociation constant of the complex. This complex formation can also be considered as lowering the pK of the second acid function, or, in other words as increasing the strength of this function. In the same way, changes in the calcium environment of excitable tissues can be interpreted as modifying the pK of some of their acid functions, and therefore changing their isoelectric point. Consequently their permeability and excitability changes in such conditions can be somewhat explained.

NICOL, J. A. C., SMYTH, C. N., and WHITTERIDGE, D. (Oxford).

Conduction velocity in relation to axon diameter in *myxicola infundibulum*.

A study has been made of the giant axon of the marine bristle worm, *Myxicola infundibulum*, Rénier, in order to determine its conduction properties. This very large axon extends through the entire length of the nerve cord, occupying one-third of its volume, and has a diameter ranging from 500 μ to 1 mm. at the anterior end, tapering to 100 μ posteriorly. It is a continuous structure without internal synapses, and gives off peripheral branches to the strongly developed longitudinal musculature in each segment. Besides varying in diameter along its length, the fibre is regularly constricted in each

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segment, about once per mm. It is surrounded by a relatively thin myelin sheath, less than 15μ thick. This axon forms the final common path for the quick reflex contractions by which the animal jerks back into its tube. It has not been possible to dissect out the axon entirely free from investing tissue but long strips of nerve cord together with a small amount of muscle and skin have been obtained.

Action potentials of this axon were amplified and recorded by means of a cathode ray oscillograph and camera. The amplitude of the action potential in a dissected nerve is about 17.5 mV. and can be picked up readily from the outside of the intact animal. The animals were usually anaesthetized with 10% alcohol to prevent movement.

A single electrical stimulus leads to the production of a nerve action potential, followed by a larger muscle potential. The nerve impulse is all or none; there is a tendency, occasionally, for repetitive responses to single stimuli. Both nerve and muscle may be fatigued by rapid stimulation, the muscle potential dropping out much sooner than the nerve potential. Sharp mechanical stimuli give rise to single impulses, resulting in separate muscular contractions. The axon conducts equally well in both directions, when stimulation is electrical or mechanical.

Conduction velocity varies from 6 to 20 m./sec., according to the diameter of the axon in the region where it is measured. Conduction velocities for a series of axons have been determined and the diameters of these axons have been measured histologically. The relation of the velocity to the diameter of the axon is discussed.

ÖBRINK, K. J. (Uppsala). The kinetic distribution of gastric acid.

The relations in gastric stimulation by intravenous injection of histamine.

It is possible to stimulate the gastric glands by histamine given intravenously if the injection is made slowly and continuously. This has been done by a motor-driven syringe. The injection rate has been varied. The experiments have been carried out on dogs with Heidenhain pouches.

After some four to six minutes the gastric juice appears but does

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not reach a steady state before twenty to thirty minutes. After that an almost constant level can be maintained for hours.

When the injection rate is changed a new constant level will be reached. The relations between the injection rate and the secretion rate is given by the equation

$$y = a(1 - e^{-kx})$$

where y = the secretion rate

x = the injection rate

a and k = constants

e = the base of the natural logarithm.

A maximal flow of gastric juice is easily obtained, a fact which ought to be kept in mind when a secretagogue or an inhibitor substance is to be tested. *Differences in the stimulating or inhibiting effect can only be discovered when the stimulation is submaximal.*

It is also seen that there is no stimulation threshold for the histamine administered. The curve passes through the origin, i.e. even very small injection rates initiate secretion.

The relations between secretion rate and acidity.

If we consider the secreted acid as being of a constant strength (the primary acidity) all variations occurring are easily explained by the diffusion theory, which considers the decrease in acidity as a result of exchange diffusion of H-ions against Na-ions. The relations between secretion rate and chloride content are also very easily explained by the diffusion theory.

The relations between secretion rate and excretion of neutral red.

Neutral red has been injected intravenously in the same way as histamine. It can be shown that the dye is not secreted by the gastric glands as is the hydrochloric acid.

The behaviour of the dye can perhaps be explained by the diffusion effect of the hydrochloric acid.

PITTS, ROBERT F. (Syracuse, N.Y.). Renal mechanisms involved in the excretion of acid urine by the normal human subject.

Normally the slightly alkaline glomerular filtrate is converted into acid urine during its passage through the renal tubules. This conversion is effected by the reabsorption of bicarbonate and by the

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transformation of the alkaline buffer components of the filtrate into their acid forms.

At plasma concentrations of bicarbonate below 25 millimols per liter, reabsorption of bicarbonate from the glomerular filtrate is essentially complete. Above 25 millimols per liter, bicarbonate is excreted in increasing quantities and the urine becomes alkaline. In three normal subjects the maximum tubular reabsorptive capacity for bicarbonate varied between 2.7 and 3.0 millimols per 100 ml. of glomerular filtrate. When more than this quantity is delivered into the renal tubules, the excess is excreted in the urine. The reaction of the urine varied from a low of pH 4.48 in acidosis induced by the ingestion of ammonium chloride to a high of pH 7.82 in alkalosis induced by the intravenous infusion of bicarbonate.

In acidosis, not only is the filtered bicarbonate reabsorbed quantitatively from the glomerular filtrate, but the alkaline buffer components of the filtrate are transformed into their acid forms more or less completely. This latter process is accomplished by the exchange of hydrogen ions formed within the tubular cells for ions of fixed base in the tubular urine. The absorption of the fixed base and the substitution of hydrogen ions for that base acidifies the urine. The acid forms of the buffers are excreted in the urine as titratable acid.

The capacity of the tubules to develop a concentration difference for hydrogen ions between blood and urine is limited. Thus, the maximum acidity of the urine in man approximates pH 4.5. At this reaction all dibasic phosphate ($pK' 6.8$) is converted into the monobasic form, over half of the creatinine ($pK' = 4.97$) is combined with strong acid, and *p*-aminohippurate ($pK' 3.83$) is partially eliminated as the free acid. When these buffers are infused into normal man in ammonium chloride acidosis, the rate of elimination of titratable acid increases in proportion to the quantity of buffer excreted. Comparing the three buffers at comparable molar rates of excretion, it is evident that the higher the pK' of the buffer, the more effectively can the kidney exchange hydrogen ions for the fixed base bound by that buffer. When phosphate was infused at high rates, the excretion of titratable acid increased to as much as 0.4 to 0.5 milliequivalents per minute and gave no evidence of any limitation. A limitation was imposed by the appearance of tetany in the subject.

DEL POZO, E. C., and ANGUIANO, L. G. (Mexico). The effects of scorpion venom on striated muscle.

The effects of saline extracts of ground telsons of *Centruroides suffusus suffusus* and *C. Noxius* have been studied on cat striated muscles. Intravenous injections of venom elicit fascicular contractions resulting from spinal activity. After spinal transection the fascicular contractions below the level of the section are more marked. These fasciculations are prevented by destruction of the cord or by section of the motor nerves. However, fascicular contractions appear when the intoxicated muscle is activated by electrical stimuli or by acetylcholine. Intra-arterial injections of venom produce abundant muscular fibrillations even in cut nerve preparations; the same effects are obtained by application of the venom on the muscle surface or by intramuscular injection. The direct application of venom to the nerve in isolated (frog) or *in situ* (cat) nerve-muscle preparations does not elicit motor effects. Fibrillations are not obtained when venom is applied to denervated muscle.

Maximal electrical stimuli applied to a poisoned muscle produce contractions of greater amplitude and duration than normally. Such responses are repetitive and show one or more additional rises in tension. This type of response may be obtained 24 hours after the injection of the venom. A gradual decrease of amplitude, duration, and repetition of the responses takes place when a series of stimulations are applied.

Three to five per second stimulation of cat gastrocnemius muscle yields initially tetanic contractions which later show individualized responses. Complete tetani are obtained with relatively low frequencies. High frequency stimulation gives rise to peculiar curves with two stages of tension rise separated by a fall, and a tension decrease (transmission fatigue) faster than normally. The curves seem to be obtained with a higher frequency of stimulation.

Scorpion venom increases the amplitude and duration of muscular responses to acetylcholine.

Decurarizing effects of scorpion venom are shown by the immediate deblocking action after paralyzing doses of curare. Anticholinesterase activity is demonstrated by inhibition of acetylcholine hydrolysis by defibrinated blood when blood-pressure effects are tested.

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Large doses of venom block the muscular responses to stimuli applied to the motor nerve, but contractions are produced by direct stimulation. This blocking effect is reversible.

REID, C. (London). Secondary effects of insulin on metabolism.

The physiological role of insulin is regarded as stimulating the preliminary reactions concerned in degrading the glucose molecule. Secondary effects are observed on protein and fat metabolism. Thus protein catabolism is spared by giving glucose to fasting animals as judged by the decreased catabolism of hepatic protein (rat) and of the decreased urinary N (dog; cat) as compared with their behaviour in completely fasted controls. No protein sparing occurs in depancreatized animals given carbohydrate.

Alanine and related deaminated residues, lactate and pyruvate, readily increase the store of liver glycogen in fasted animals (rat), but exogenous insulin given with alanine or the 3 C atom residues prevents the formation of liver glycogen. The protein sparing action of carbohydrate may thus be secondary to a checking of the rate of entry of sugar forming residues into the chain of reversible reactions concerned with the disposal of glucose and of the 3 C atom compounds. Further, exogenous insulin in a dose sufficient to cause mild hypoglycaemia produces a small decrease in the metabolic rate and in the R.Q.

As regards fat metabolism exogenous insulin given to a normal cat fasted 48 hours does not inhibit fat metabolism because as stated previously the metabolic rate decreases slightly with a mildly hypoglycaemic dose of insulin and increases slightly with a more decided hypoglycaemic reaction. On the other hand carbohydrate combined with exogenous insulin raises the R.Q. significantly in the fasted cat and the metabolic rate slightly. Evidently under these conditions, i.e. carbohydrate oxidation, the entry of fatty acid residues to the oxidative pathways is checked and fat metabolism declines.

ROSE, BRAM (Montreal). The synergistic action of histamine and anti-histamine compounds on isolated smooth muscle.

During the course of investigations on the relative potency of various anti-histamine compounds assayed by their ability to prevent smooth muscle contraction due to histamine, it was noted that large doses of an anti-histamine compound (*n*-Pyridyl, *n*-Benzyl, Dimethylethylenediamine monohydrochloride) were not capable of producing a contraction of the smooth muscle, whereas a combination of this compound with histamine was active in this respect. It was thus found that a piece of gut inhibited by a small amount of the anti-histamine compound would not contract on the addition of either histamine or the anti-histamine compound when either of these were added separately to the bath. A combination of histamine with a large amount of anti-histamine compound was, however, capable of producing a marked contraction and an equivalent amount of the anti-histamine compound by itself was inactive. The significance of this finding will be discussed.

SKOGLUND, C. R. (Stockholm). Reciprocal effects due to stimulation of the spinal cord by currents of opposite direction.

The effects of stimulation of the cord with direct currents of various duration have been studied in experiments on decerebrated cats. The stimuli were applied (through surface electrodes or inserted needle electrodes) to the lumbar cord or to descending tracts in the medulla oblongata and the responses were recorded from motor roots or different nerves and muscles of the hind leg.

The typical responses of central nervous structures to artificial stimulation with direct currents are described and the similarity to natural discharges is emphasized.

When the electrodes are placed on the lumbar cord in a given position it is found that stimulation with gradually increasing current strength in one direction causes flexor responses, while extensor responses predominate when the current is reversed. Monopolar stimulation of the descending tracts in the medulla evokes selective activation of the extensor system when the inserted electrode is made positive, while flexor responses occur when the electrode is negative.

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In order to analyse the mechanism of this selective excitation the excitability of the two systems has been studied during constant polarization.

This method of activation of opposite systems in the cord has been applied in investigations on spinal reflexes (in collaboration with *Bernhard*) and some results from these investigations are also reported.

SMITH, W. W. (Bethesda, Md.). The effect of protein and sulfur-containing compounds on the physiological response to methyl chloride.

The toxicity of methyl chloride was investigated during the war because of potential hazards from repeated exposures to low concentrations. The influence of dietary factors on the response of rats, exposed to 2,000 p.p.m. 6 hours a day, 6 days a week from the age of 6 weeks until death, is reported here.

Increasing casein from 20 to 35% lengthened survival time of 50% of the group (LT₅₀) from 10 to 29 days, while with 47 or 60% casein the LT₅₀ dropped to about 24 days. Decreasing casein to 9 or 4% did not change the survival time, which remained about 10 days.

Cystine or methionine supplementing diets containing 4 to 20% casein increased survival time by about 12 days per meq. supplementary sulfur per 100 gm. diet, far more than was anticipated from the results with increased casein. Equal supplements with higher casein diets provided less protection, usually 1 to 5 days per meq. 20% lactalbumin was equivalent to 20% casein supplemented to equal cystine. A casein digest (amigen) was as effective as casein in reducing the potential protective action of the sulfur-containing amino acids.

Sodium thiosulfate, sodium sulfate, and sodium sulfide were without effect, as was cystine betaine, a compound thought to undergo no metabolic changes. BAL (0.2% in the diet) gave marked protection to half of the group, while 1.3 dimercaptopropanol had little if any influence.

In most diets l-cystine and dl-methionine, as based on sulfur equivalence, were equally effective in prolonging life, and on some of the well-supplemented diets exposed rats grew as fast as the

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controls, to within a few days of death. All supplements, however, failed to prevent the development of a neurological syndrome involving principally the hind legs.

The relationship between sulfur-containing amino acids and protein in protection against the lethal effect of methyl chloride is probably modified by maintenance requirements at casein levels below 20%, where growth is sub-optimal. This interpretation is supported by reports of others in connection with the lipotropic action of methionine and the development of hemorrhagic kidneys on choline-deficient diets. It cannot, however, account for the failure of casein-methionine to give protection equal to supplementary methionine at levels above 20% casein where growth and sulfur intake were equal. Such observations indicate the possibility of amino acid competition for a common enzyme system, for which we are now seeking independent evidence.

TAINTER, M. L., BECKER, T. J., and MILLER, L. C. (Rensselaer, N.Y.). **The quantitative evaluation of spasmolytic drugs in vitro.**

For many decades the *Magnus* method has been used for recording the reactions of excised tissue to spasmolytic drugs added to the surrounding physiological solution. During this period no method has found universal favor for expressing the potency of active compounds in terms of comparable well-known standard drugs such as atropine or papaverine. Our method consists of producing musculo-tropic spasms in excised rabbit ileum by barium chloride or in guinea-pig ileum by histamine. The spasmolytic effect of papaverine against these spasms is set up as a standard response. Similarly, atropine is taken as the standard against neurotropic spasms induced in rabbit ileum by acetylcholine. Each strip can be used four to six times. The spasmolytic drug is added to the tissue bath to give three different concentrations such that about 25, 50, and 75% respectively, of eight trials at each level are positive. Positive effects are those trials in which the added drug relaxes the muscle to one-fourth the tonus level existing in spasm. Thus it is possible to regard the relaxation of the induced spasms as an all-or-none (quantal) phenomenon. A linear relationship exists between log-concentration of the spasmolytic

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lytic drug and the probit (probability unit of Bliss¹) corresponding to the proportion of positive effects. Dosage-effect data for both the standard (atropine or papaverine) or test drug are plotted on log-probit graph paper.² Parallel lines best fitting both sets of points are drawn by eye. From these lines the potency of the test compound may be estimated. By appropriate conventional methods³ the standard error of this potency estimate can be calculated. Using the above method a single, definite (most probable) potency value can be determined for each spasmolytic drug along with an index to the reliability of that estimate. This method has been found practical in screening for spasmolytic activity on an extensive scale.

¹ Bliss, C. I., *Science*, 79, 409-10 (1934). ² Miller, L. C., and Tainter, M. L., *Proc. Soc. Exp. Biol. and Med.* 57, 261, 264 (1944). ³ Gaddum, J. H., *Med. Res. Council Spec. Rep. No. 183*, His Majesty's Stationery Office, and Bliss, C. I., *Ann. Appl. Biol.* 22, 307-33 (1935).

TEORELL, TORSTEN (Uppsala). Bio-electrical polarization studies by means of square wave currents.

It is well known that the polarization of tissues can appear as variations in the impedance towards A.C. of different frequencies or as changes in the tissue potential. In recent years impedance measurements with A.C. have been frequently employed for the characterising of the polarization behaviour. A new method employing square wave currents instead of sinusoidal currents makes it possible to record impedance changes of a very short duration, which appear in tissues, for instance after brief electrical stimuli. The results may be expressed either as a 'time-current strength' relationship or, as in this communication, in terms of an 'equivalent scheme' based on resistances and a 'polarization capacity' (impedance loci diagrams).

Excised surviving frog skin has been employed as a tissue, the inside being bathed in a nutritional solution, the outside subjected to various electrolyte solutions. The skin could also be electrically 'stimulated' by aid of Ag-Pt electrodes placed across the skin. The skin potential was measured via calomel electrodes. The 'square wave analysis' employed has been recently described.¹ Some experiments are described. (1) Ringer, NaCl, KCl, and CaCl₂ have been

compared as outside solutions. They increase the D.C. resistance (i.e. the 'polarization resistance') and decrease the potential in the order given. The changes of the polarization capacity will be discussed. (2) Rectifying properties of the skin can be demonstrated. (3) The influence of the strength, duration, and current direction of D.C. stimuli has been studied. Most stimuli will cause a temporary decrease of the D.C. polarization resistance (the high frequency resistance stays constant). The polarization capacity seems, however, to remain unaltered. There are, in general, marked differences in the effects of 'anodic' and 'cathodic' stimulation, in particular as regards the skin potential.

The frog skin results have been compared with polarization phenomena and potentials exhibited by some artificial membranes as studied by the present technique. It seems probable that a great deal of what is here termed as 'polarization' can be related to ionic distribution phenomena across charged membranes.

¹ *Acta Physiol. Scand.* 12, 235 (1946).

THERMAN, P. O. (Helsinki). Reciprocal excitability changes in mammalian A nerve fibers.

The excitability properties of cats' sciatic nerves, excised and soaked in Krebs-solution at pH 7.4 and stabilized to a moist atmosphere of $\text{CO}_2\text{-O}_2$ at 38°C ., have been studied with respect to low and high threshold A fibers. Alkaline or acid shifts induced by increasing amounts of O_2 , N_2 , or CO_2 resp., of the gas mixture in the nerve chamber, may cause opposite excitability changes in low and high threshold fibers of a mixed nerve. The effects are reversible and accompanied by changes in after-potentials as well as membrane potential of the nerve. In pure motor nerves corresponding excitability changes are of an opposite nature in flexor and extensor nerves. Thus, an increase of excitability of low threshold fibers in a flexor nerve is followed by a simultaneous decrease of excitability in corresponding extensor nerve fibers. These opposite effects are assumed to have a functional significance in the reciprocal innervation of antagonistic muscles. Similar reciprocal effects have not been found in pure sensory nerves, flexor or extensor in origin.

WALAWSKI, JULIAN (Warsaw). The different physiological states of the vagus nerve's activity in clinical observations.

In my experiments on animals published in my former papers, I have found that the pneumogastric nerve, apart from the normal status can show a hypertonic, an excited as well as a paralytic state which may be provoked by means of the electric current or by pharmacological agents.

A different pneumogastric condition finds its expression in a different electrocardiographic curve, and also as demonstrated by *Czubalski*, in characteristic blood changes.

I have found that in exanthematic typhus the state of the vagus nerve may vary. Electrocardiography and blood protein analysis in exanthematic typhus patients carried out during the 1940-5 epidemic in Warsaw showed that at the very beginning of that disease there are manifestations of hypertonic or excited conditions of pneumogastric nerve. They are of a very short duration. In the full fever period there appears paralysis, whereas in the defervescence and in apyrexia the excitation or hypertonicity of the vagus is observed. These vagus activity changes are in relation to the blood circulatory troubles in its centre, provoked by capillary changes due to the typhus *Rickettsia*.

Experiments have shown that in the full fever period the vagomimetic remedies, such as ergotaminol (gynergen Sandoz) and atropin, give no effect whatsoever due to the lack of acetylcholine. However, they prove efficacious as soon as temperature becomes normal and the pneumogastric nerve after restoration of the circulatory condition in its centre regains its capacity of producing acetylcholine.

The pneumogastric excitation manifests itself in the heart in blocks or bradycardia with a low T wave in the electrocardiographic curve, and in the blood by the decrease of the serum protein.

Pneumogastric hypertonicity provokes the bradycardia with a T wave elevation and a serum protein increase.

The results of serum protein evaluations in the exanthematic typhus were published in the proceedings of the Polish Academy of Science in Cracow in 1946. The results of electrocardiography are now in printing.

The different vagus tonus condition in the exanthematic typhus

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taken together with clinical symptoms has given a new starting point to an original pathogenic conception published by myself in collaboration with *Gerner* (Warsaw, 1946) in a monograph on exanthematic typhus.

VON WENDT, GEORG (Helsinki). **Observations concerning A- and C-vitamin metabolism and their relation to the power of resistance.**

During the First World War many observations were made which showed the significance of the vitamin supplies for the power of resistance.

In a Norwegian officers' battalion with a body of selected men the morbidity of tuberculosis rose in 1916 from a few tenths % to 3.5%, when the potatoes included in the food lost their C-vitamins by being boiled too long, and when condensed milk and margarine were substituted for whole milk and butter in 1921 the morbidity increased to 6.1%. The correction of the errors in connexion with the lecturer's studies of similar cases during the World War, led in 1928 to the disappearance of tuberculosis.

These observations led to self-experiments of long duration in order to study the A- and C-vitamin metabolism. The researches of *Giroud* concerning the significance of the C-vitamin for the working-readiness and working-results of guinea-pigs, as well as the researches of the same scientist concerning the influence of strenuous labour on the C-vitamin percentage in the cortex of the suprarenal gland helped considerably in the clearing up of the problems.

Through the self-experiments:

1. an increase of the deficiency of C-vitamin by increased use of the muscles; and
2. an increase and a decrease of the deficiency of C-vitamin in proportion to a better or worse supply of A-vitamin.

Against the background of the studies of *Giroud* this shows that extensive syntheses of C-vitamin occur in the human body and that their extent, as with the animals, is dependent on the extent of the supply of A-vitamin.

At the beginning of muscular work the C-vitamin syntheses are stimulated primarily by a hormone secretion from the cortex of the

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suprarenal gland, whereby C-vitamin is consumed. At an insufficient content of the cortex of the suprarenal gland with C-vitamin this hormone secretion can only ensue more or less imperfectly, causing a greater or smaller deficiency of C-vitamin. The content of the cortex of the suprarenal gland with C-vitamin depends on the supply of A-vitamin. On account of the altogether too scanty supply of A-vitamin in the ordinary food in the civilized countries the content of the cortex of the suprarenal gland with C-vitamin is scarcely one-seventh of the normal.

The average content of the cortex of the suprarenal gland with C-vitamin is about 140 mg.% in animals. According to reliable analysis material, the average percentage in adults is only 20 mg.%. In normal human foetuses the C-vitamin percentage in the cortex of the suprarenal gland is about 140 mg.%.

The charging of the cortex with C-vitamin gives simultaneously a picture of the status of the power of resistance of the resisting apparatus. The diminished percentage of A- and C-vitamins of the Norwegian officers' battalion caused such a further decrease in the power of resistance, that many otherwise harmless tuberculous infections were able to flare up. The lecturer has recently been able to make similar observations in regard to cancer.

On a constant diet with an insufficient supply of C-vitamin the C-vitamin deficiency can be diminished to a certain point by increased supply of A-vitamin. The quantity of A-vitamin needed for this is equal with the individual's A-vitamin requirements. As a rule these requirements are never below 15,000 international units of A-vitamin. The need of the lecturer is at present at 18,000 I.U.

WIERZUCHOWSKI, M. (Lodz, Poland). On the maximum and the optimum level of glucose utilization in the mammalian body.

When glucose is being introduced intravenously at constant rate at some blood-glucose concentration, a peak of utilization appears which also is the optimum of assimilation, because with a further rise in blood-glucose a decrement of utilization follows, as is evident from the data:

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Condition of the animal during continuous glucose injection	Maximum and optimum level of utilization		When blood glucose further raised a drop of utilization of gm./sq. m. ¹ per hour
	Increase of blood glucose above the pre-injection level mg. %	Glucose utilized gm./sq. m. ¹ per hour	
1. Normal dog, resting . . .	945	97	11
Adrenaline 0.03 mg./kg. an hour	762	49	16
2. Normal dog, resting . . .	977	88	7
3. " " " . . .	1,178	87	17
4. " " " . . .	1,170	75	10
Other normal dogs, resting . . .	640	83	25
Work, 1,000 kg.m./kg./hour . . .	1,000	107	16
Work, 1,200 " " " " . . .	1,105	128	11
Chloralose anesthesia, dog . . .	641	99	16
Amytal-sodium anesthesia, dog			
Body temperature below 37° . . .	499	62	10
" " 37-39° . . .	759	83	14
" " above 39° . . .	1,035	99	—
Insulin (high dosage) . . .	538	74	29

¹ Cowgill and Drabkin's surface area formula for dogs.

WIERZUCHOWSKI, M., SYSA, J., and TOCZYSKI, T. (Lodz, Poland). Respiratory center under influence of excessive hyperglycemia in dogs under chloralose anesthesia.

During progressive intravenous saturation with glucose of the intact dog or of the isolated head preparation the respiration rate remains in many cases constant up to almost the highest blood-glucose levels and only the depth of each breath increases with the concentration of blood-sugar. Up to 3,000 mg. %¹ of blood-glucose, carbon dioxide inhalation causes the usual stimulation of respiration; between 3,000 and 4,000 mg. %, however, this reaction decreases. Between 3,300 and 3,700 mg. % the increased vulnerability of the center appears: short lasting, and up to this concentration harmless, asphyxias often become lethal. The reflex excitability of the center (from pressoreceptor areas, by direct stimulation of the carotid sinus nerve or of the central end of the cut vagus) persists up to the high levels of hyperglycemia, but at last ceases as a premonitory sign before the final

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refusal of the respiratory center. In many cases the medullary and spinal respiratory centers die between 3,500 and 4,200 mg.%, after suffering some depression of the respiration rate and amplitude. But sometimes, even in the absence of chemoceptor tissue, they still retain their activity up to markedly higher levels: 4,550 mg.% (medullary) and 4,750 mg.% (spinal). As in anemia,² they appear to be more resistant to the extreme hyperglycemia than other centers.

¹ In the venous blood; arterial blood glucose content is several hundred mg.% higher. ² Heymans, C., and Bouckaert, J. J., *Bull. de l'Acad. royale de méd. de Belg.* 3, 29 (1938).

ZELLER, E. A. (Basel). On the chemistry of the ophio-l-amino acid oxidase and its application to the estimation of peptidases.

Ophio-l-amino acid oxidase¹ does not attack N-substituted amino acids and imino acids like Prolin.² The velocity of the oxidation is a function of the chain length of the substrate. The enzyme has been found in the lung and liver of venomous and non-venomous snakes³ and in the venoms of more than 20 species. No trace of the enzyme was found in the venom of *Bothrops itapetiningae* which is pure white, while the other venoms are yellow and contain riboflavin.

As soon as a greater amount of snake venom was available (*Bitis gabonica*), the purification of the enzyme was undertaken. The various steps of the procedure and some properties of the purified substance will be described.

Since the Ophio-l-amino acid oxidase oxidises only free amino acids and no peptides, the enormous activity of the enzyme can be used for the qualitative and quantitative estimation of several peptidases in different biological sources. Under suitable conditions the velocity of reaction is a constant, which only depends on the activity of the peptidase. Some details and results of this method will be discussed.

¹ Zeller, E. A., and Maritz, A., *Helv.* 27, 1888 (1944). ² Zeller, E. A., Maritz, A., and Iselin, B., *Helv.* 28, 1615 (1945). ³ Zeller, E. A., Iselin, B., and Maritz, A., *Helv. Physiol. Acta*, 4, 233 (1946).

BERITOFF, J. (Tbilisi, U.S.S.R.). The origin and biological significance of the electric potentials of the spinal cord.

The initial rapid potentials, led off from the surface of the spinal cord of the cat and frog or from the dorsal roots with the stimulation of sensory nerves, represent an expression of the excitation of the intraspinal piece of the dorsal-root fibres. The fairly short discharge of rapid potentials following after them for a period of one-tenth of a sec. or a little more arises as a result of the excitation of the internuncial circuits.

The rapid potentials led off from the ventral roots express the excitation of ventral-root fibres. In certain cases the rapid potentials of large amplitude that arise immediately after the dorsal-root effect express the excitation of motor neurones directly evoked under the influence of the dorsal-root impulses.

Slow potentials, led off from the surface of the cord and also from the dorsal and ventral roots, result from the summation of the electrical potentials of the local processes arising in the dendrite and cellular mass of the gray matter of the cord (neuropil) in the region of the synapses of the dorsal-root fibres, internuncial neurones, and recurrent collaterals of the motor neurones. The slow potentials, led off from the dorsal roots, express the local processes of the neuropil chiefly of the dorsal half of the corresponding segment, and those led off from the ventral roots express the local processes of the ventral horn of the corresponding segment.

The biological significance of the rapid potentials consists, in the first place, in the conditioning of the transmission of impulses of excitation from the dorsal-root fibres to the internuncial and motor neurones and, in the second place, in the production of local processes in the dendrite and cellular mass leading to the formation of slow potentials.

The biological significance of the cellular slow potentials lies in the prolonged excitation of corresponding axons as a result of the stimulating action of these potentials.

The biological significance of the dendrite slow potentials consists, chiefly, in the anelectrotonic decrease of excitability in the nearest axon and cellular elements, which thus conditions weakening of their excitation and blocking its transmission from neurone to

neurone. This depressing action of the slow potentials expresses central inhibition and lies at the bottom of the general inhibition arising with every active condition of the central nervous system.

BEZNÁK, ALADÁR, B. L., and GÁSPÁR-RÁDY, Zs. (Tihany, Hungary). Observations on the mechanical response of frogs' rectus and sartorius to nervous and acetylcholine stimulation.

These muscles respond to electric stimuli (ES) of varying frequencies (10–100/sec.) and intensities (0.5–50 μ F) as well as to acetylcholine solutions (AC) of varying concentrations (0.01–20,000 μ g./ml.) with tetani. The 'quick phase' of *Brown* previous to the tetanus is seen only in the sartorius. Height and duration are positive exponential functions of the concentration of AC (as described by *A. J. Clark*) or of the intensity of the ES. Higher concentrations of AC, or greater intensities of ES can elicit contraction from both rectus and sartorius after the muscle has relaxed its tetanus developed in a more dilute AC bath or during the continued stimulation by a weaker ES provoking less than 80% of the maximum contraction. Following relaxation of tetanus in an AC solution, or ES causing 100% contraction, no increase in the intensity of the ES or in the concentration of the AC can cause the muscle to contract. The force necessary to stretch the muscle in tetanus of a given height back to resting level is the same whether the tetanus is caused by ES or AC.

Both oxidizing (bubbling of O_2 , oxidized glutathione, &c.) and reducing (bubbling of H_2 , reduced glutathione, adrenaline) agents strongly but reversibly depress, or suspend the excitability of the muscle by ES or by AC. Contrary to AC, salts of adenosinpyrophosphate (ATP) do not imitate the ES.

The available experimental data are best in accord with the hypothesis that muscle contains a population of nerve endings of various excitability liberating AC and of receptors of varying sensitivity to AC. Contraction is brought about by the reaction of the receptors with the AC. AC liberators and receptors both become refractory after action. The time of recovery also varies. Redox-processes play a role in the building up of the sensitivity to AC of the receptors.

BEZNÁK, MARGIT, and HAJDU, ISTVÁN (Tihany, Hungary). The role of extra-cardiac factors in mechanical heart hypertrophy.

By narrowing the ascending aorta of white rats, a heart hypertrophy can be obtained which is demonstrable in 2 days, well pronounced in a week, and about doubled in 4 weeks. The heart was found to be unable to hypertrophy in consequence of the narrowing, if the pituitary had previously been extirpated, but the hypertrophy was again present after the implantation of the first lobe of the pituitary. The extirpation of the stellate ganglia on both sides caused the hearts of white rats to increase in weight. This increase is present proportionally in all the parts of the heart. In the majority of cases the weight-plus was gained by the 8th day. The narrowing of the ascending aorta produced a hypertrophy of the left ventricle in normal, and in rats whose stellate ganglia had at different times previously been extirpated. If the narrowing is carried out at a time when the gain in weight caused by stellate ganglia extirpation had already taken place, there is—beyond this—a left-ventricle hypertrophy of the same extent as in normal animals. Histological findings of above experiments are discussed.

COMLINE, R. S. (Cambridge). Synthesis of acetylcholine by non-nervous tissue.

Saline extracts of acetone-dried nervous tissue form large amounts of acetylcholine in the presence of cysteine, choline, NaF, KCl, Mg. ions, and, in addition, adenosinetriphosphate (ATP), citrate, and a dialysable, heat-stable substance called the 'activator', prepared by boiling saline extracts of acetone-dried brain (for references see *Feldberg and Mann, 1946*). Synthesis under similar conditions has now been studied in organs other than those of the nervous system, particularly the human placenta and the spleen of the horse, which are known to contain large amounts of acetylcholine.

Human Placenta: Placental extracts form, aerobically and anaerobically, large amounts of acetylcholine (up to 1 mg./g./hr.) in the presence of ATP, citrate, and activator. In general, synthesis of acetylcholine by placental extracts differs from that by brain extracts in the following ways; with brain extracts the synthesis of acetyl-

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choline is greatly enhanced by citrate; with placental extracts citrate has only a small effect; on the other hand activator has a much more pronounced effect on placental extracts than on brain extracts.

Spleen: Extracts from acetone-dried horse spleen form between 15 and 40 $\mu\text{g./g./hr.}$ in the presence of ATP, citrate, and activator. These values may not represent the true ability of the spleen to form acetylcholine as the extracts contain a powerful inhibitor of acetylcholine synthesis by brain and placental extracts. This inhibitor is non-dialysable and thermolabile; its action is reduced by the addition of boiled brain extract.

Heart: Of other non-nervous tissues only the auricle of the heart (dog) formed appreciable amounts of acetylcholine (up to 90 $\mu\text{g./g./hr.}$); extracts from the ventricle of the heart only formed between 5 and 20 $\mu\text{g.}$ acetylcholine.

Effect of Flavine-adenine-dinucleotide (FAD): The relatively small amounts of acetylcholine formed by placental extracts in the absence of activator were greatly increased by the addition of FAD. In general, the accelerating effect of FAD on the synthesis of acetylcholine by placental extracts was about 70% of that produced by the addition of boiled brain extracts. This strong effect of FAD was dependent on the presence of both citrate and Mg. ions. The effect of FAD on the synthesis of acetylcholine by brain extracts was neither so pronounced nor so regular as that on placental extracts and much smaller than that of boiled brain extracts.

It is probable that the action of FAD is separate from that of the 'activator' of *Feldberg* and *Mann* (1946), which appears to be identical with the 'coenzyme of acetylation' studied by *Lipmann* (1946) and by *Nachmansohn* and *Berman* (1946).

Feldberg, W., and Mann, T., J. Physiol. 104, 411 (1946). *Lipmann, F., Adv. in Enzymol.* 6, 231 (1946). *Nachmansohn, D., and Berman, M., J. Biol. Chem.* 165, 551 (1946).

COOPER, K. E., GREENFIELD, A. D. M., HUGGETT, A. ST. G.,
and KERSLAKE, D. MCK. (London). A method for measuring the rate of blood flow in the umbilical cord.

The rate of blood flow in the umbilical cord has been measured in the sheep foetus, delivered by Caesarian section under spinal anaesthesia.

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The measurement depends on the principle that if the umbilical veins alone are occluded, the rate of diminution of foetal volume is the rate of blood flow in the umbilical arteries. Evidence is presented that during the initial period of such occlusion, the dynamics of the foetal circulation are not appreciably disturbed, and that in this period the rate of flow in the umbilical arteries is unlikely to be altered.

The foetus is completely, and the mother partly, immersed in a large saline bath at 38° C. throughout the experiment. The foetus is enclosed in a dish-shaped plethysmograph, filled with saline to the same level as the bath in which it is immersed. The lid of the plethysmograph is formed like a shallow bell, the brim of which dips into the saline, covering nearly the entire surface. The cord passes under the brim, and out over the side of the plethysmograph, and no packing is therefore required to seal its point of entry. Observed foetal volume changes alter the saline level in the plethysmograph by less than 1 mm., and when the umbilical veins are occluded, passage of blood out of the plethysmograph along the umbilical arteries withdraws an equal volume of air from a balanced volume-recorder into the space under the lid. The apparatus as a whole is dynamically calibrated over the whole range of flow rates; measurements are accurate to within $\pm 10\%$.

A section of the umbilical cord between the plethysmograph and the placenta can be subjected to various pressures by means of a pneumatic bag. Pressures less than 30 mm. Hg. generally fail to occlude completely the veins in the cord. Pressures over 50 mm. Hg. constrict the arteries. Between these limits there is for each foetus a range of 10–15 mm. Hg. over which the initial rate of flow in the arteries is both maximal and constant, and is equal to, or very slightly less, than that which follows digital occlusion of the veins only. The last finding makes it unlikely that the bag pressure seriously affects the arterial flow. The rate of flow in the umbilical arteries is constant for the first 2–3 seconds of venous occlusion; the foetal heart rate and umbilical arterial pressure are not significantly altered from their resting values.

It is concluded that the initial rate of blood flow following venous occlusion is unlikely to be different from the resting rate. The initial rate is therefore used as a measure of the rate of blood flow in the undisturbed umbilical cord.

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COOPER, K. E., GREENFIELD, A. D. M., HUGGETT, A. ST. G.,
and KERSLAKE, D. MCK. (London). **Umbilical blood flow
in the foetal sheep.**

The foetal plethysmograph shows that the foetal volume remains constant to within 2-3 c.c. for long periods if care is taken not to interfere with the cord. This indicates a very constant partition of the blood volume between foetus and placenta.

The resting blood flow determined on a single foetus at short intervals is fairly constant, and fluctuations of 20% above or below the average value are unusual.

The flow is considerably reduced by handling the cord. Needling the vessels, particularly the veins, may cause a diminution of flow to less than half, and complete recovery has never been observed. By spraying 10% formaldehyde in normal saline on part of the cord (Barcroft, 1946) it has been possible to insert needles into an artery and vein simultaneously, and leave them in position without causing significant change in the blood flow.

This has enabled simultaneous samples of arterial and venous blood to be collected under conditions of demonstrably normal placental circulation. A few determinations of foetal oxygen consumption have been made by measuring the arteriovenous oxygen difference under these conditions.

The variation of umbilical blood flow with foetal age and weight is shown in the table.

Foetus No.	Foetal Age in Days	Foetal Weight in Grams	Umbilical blood flow c.c. per minute	
			Range	Average
154 T	100	630	60-126	90
174	105	739	120-150	138
141	115	1,722	205-305	170
165	121	1,791	175-235	210
126	125	2,109	210-300	270
151 T	134	2,120	235-330	285
162	130	2,179	180-280	240
183 T	143	2,480	185-285	230
136	130	2,600	220-365	280
194	143	4,200	340-490	440

NOTE.—T indicates that foetus is one of twins.
The second foetus in No. 183 was shrivelled
and partly absorbed.

CORBOZ, J. ROBERT (Fribourg, Switzerland). **Quelques notions nouvelles d'hémodynamique.**

Le théorème de *Bernoulli* dit que dans une conduite parcourue par un fluide parfait la somme de la hauteur piézométrique, de la hauteur due à la vitesse et de celle de la cote du point est la même pour tous les points. Or le sang ne répond aucunement aux conditions d'un fluide parfait: si sa compressibilité est relativement faible, sa viscosité joue par contre un rôle déterminant dans la chute de pression tout au long du torrent circulatoire.

Le coefficient de viscosité intervient quantitativement à un degré différent suivant le caractère du courant: turbulence de *Reynolds* ou écoulement de *Newton*. Nous ne considérerons que ce deuxième cas

dont l'équation fondamentale est la suivante: $\tau = \mu \frac{du}{dy}$

L'énergie τ nécessaire pour vaincre le frottement entre deux lames liquidiennes est proportionnelle à la variation de vitesse du courant entre elles du pour une distance donnée sur l'ordonnée dy , ainsi qu'au coefficient de viscosité du liquide μ . Abstraction faite de son segment aortique, le courant sanguin répond à l'équation de *Newton*. On l'a souvent assimilé jusqu'ici à l'écoulement laminaire de *Poiseuille*. Or celui-ci n'est qu'un cas particulier dans le cadre du courant de *Newton*. Il est réalisé lorsque le profil des lignes de courant devient parabolique, phénomène se produisant par exemple par écoulement d'un fluide homogène dans des conditions où le nombre de *Reynolds* soit inférieur à 1,100.

Quant au sang, nous devons le considérer comme un liquide doublement hétérogène: il représente en effet une émulsion de globules dans un plasma dont les molécules sont de poids fort différents. Ses propriétés physico-chimiques influencent son mode d'écoulement, dont les bases théoriques n'ont pu être jetées avec certitude jusqu'à ce jour. Afin de pouvoir utiliser quand même la formule de *Poiseuille* nous avons recours à un artifice qui consiste à remplacer le facteur μ par μ' , celui-ci n'étant valable que pour une concentration en globules, une vitesse de courant et un calibre vasculaire donnés. Les recherches expérimentales de notre Institut démontrent, paradoxalement à première vue, que c'est au niveau des capillaires que la valeur de μ' atteint un minimum.

COURTICE, F. C., and GUNTON, R. W. (Oxford). The determination of the blood volume by the Evans blue and carbon monoxide methods in man and rabbit.

Since the introduction of Evans blue (T-1824), the dye method of determining the blood volume has largely superseded the carbon monoxide method. More simple and accurate means of determining the CO content of the blood (*Scholander and Roughton, 1943*)¹ now makes the CO method much easier. We have therefore reinvestigated this method and compared our results with simultaneous determinations using Evans blue.

Recently, *Root, Roughton, and Gregersen (1946)*² have used an open circuit technique for determining the blood volume by CO. This involves the accurate determination of the CO in expired air as well as the CO in blood. We have reverted to the closed circuit consisting of a Krogh spirometer (4 litres for man and 150 c.c. for rabbits) with soda lime absorber and inspiratory and expiratory valves, oxygen being admitted at intervals. The CO was determined in the blood by the method described by *Scholander and Roughton*.

The main difficulty with the CO method has been the fall in CO content of the blood as the subject continues rebreathing, the fall being due probably to CO being taken up by muscle myoglobin or red cells not normally in circulation, e.g. in the spleen. By keeping the CO level in the blood at about 2 c.c.%, this fall is not great in 1 hour. The average CO content of six experiments with human subjects at 0, 5, 10, 15, 30, 45, and 60 min. was 0.40, 2.04, 2.02, 1.97, 1.92, 1.88, and 1.86 c.c.%. Thus if the mean of the 5 and 10 min. samples be taken, the error introduced by loss of CO from the circulating blood must be small. Similar results have been observed with rabbits.

This CO method has been used simultaneously with the Evans blue method. The dye in the plasma was determined after extraction with butyl alcohol (*Harington, Pochin, and Squire, 1940*).³ The ratios of blood volume determined by the two methods, CO:Dye, were 1.04, 0.96, 1.02, and 0.95 in four human subjects and 0.95, 1.02, 1.10, 1.05, 1.02, 1.03, and 1.00 in seven rabbits. The two methods thus agree fairly closely, usually within about 5%.

The advantages of the CO method are that only small samples of

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blood are required, haemolysis in a sample does not matter, and the blood volume can be determined many times in the same individual provided enough time has elapsed for most of the CO to be eliminated. With the dye method slight haemolysis causes a significant error and repeated injections are likely to give the subject a bluish-green tint.

¹ Scholander, P. F., and Roughton, F. J. W., *J. Biol. Chem.* **148**, 551 (1943).

² Root, W. S., Roughton, F. J. W., and Gregersen, M. I., *Amer. J. Physiol.* **146**, 739 (1946).

³ Harington, C. R., Pochin, E. E., and Squire, J. R., *Clin. Sci.* **4**, 311 (1940).

COSIN, R. (Madrid). The gaseous metabolism of platelets measured by the Warburg method.

When studying the metabolism of the red cells and leucocytes the difficulty of obtaining a perfectly homogeneous material out of the blood was noticed, owing to the diversity of the cells. On the other hand, there is a difference in the specific weight of every cellular group. According to *Löhner*, specific weight values of 1.114 in the red cells, 1.075 in the leucocytes, and 1.050 in the platelets are to be found in horse blood.

The best method for the separation of each cellular group is by centrifuging and then the recount of each group after this operation.

It is possible to separate the platelets with some sureness and to obtain quite homogeneous suspensions through centrifuging during 5 to 10 minutes at 1,000 revolutions.

In this way one can obtain suspensions that contain only 200 to 300 leucocytes per c.c. as well as 15 to 20,000 red cells. The suspensions of this type have some 10% of impurities.

The metabolism that could be seen in the platelets is very small, which permits one to suppose that the impurity of the suspensions by the platelets does not form any large error in the determination of the metabolism of other cellular groups.

The normal blood was studied, taking from it 75 c.c. and diluting it with 25 c.c. of Ringer-citrate-glucose solution and centrifuging it in a fractionary way during 5 or 10 minutes. Then the suspensions of the mentioned type of impurity were chosen from it.

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Temperature: 37°; Gas: CO₂ in oxygen; Dry weight: 2 Mg.

H	6 c.cm.	2 c.cm.
B	0.1 c.cm. Lactic Ac. $\frac{m}{20} = 120 \text{ m}^3$	0.1 c.cm. Lact. Ac. $\frac{m}{20} = 120 \text{ m}^3$
V _R	6.1	2.1
V _G	6.69	11.7
KO ₂	0.60	1.04
K _{CO₂} ^R	0.92	1.14
K _M	2.07	1.89
K	0.58	0.08
60'	H = 6	h = 6
	QO ₂ = 0.51	
	Q _M ^{O₂} = 0.27	

DUYFF, J. W. (Leyden). Reflex influence of conditions prevailing in muscle on the excitability of its motor nerve.

A report is given on experiments made on the gastrocnemius muscle and the sciatic nerve of the frog, in which the influence of the initial tension of the muscle and of muscular fatigue on the excitability of the muscle itself and on that of its motor nerve were studied. Among other things it was found that:

1. The time-constant of the curarized gastrocnemius is less as the tension to which the muscle is subjected is higher.

2. As long as the spinal reflex mechanism is intact, an increase of the initial tension of the muscle is followed by a decrease of the time constant of the nerve supplying it as well as of the contralateral sciatic nerve.

3. Section of the rami communicantes does not interfere with these phenomena.

4. Muscular fatigue is accompanied by an increase both of the intensity threshold and the time constant of excitation. When fatigue is well developed, the energy curve shows two minima, indicating the presence of two types of fibres, reacting differently to exertion.

5. As long as the spinal reflex apparatus is intact, muscular fatigue results in a transient decrease, followed by a progressive increase, of the threshold and the time constant of the motor nerve supplying the muscle. The excitability changes of the nerve are absent after section of the rami communicantes.

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6. On the opposite side, the nerve exhibits a notable increase of the time constant, while the threshold changes little.

7. With indirect excitation (and, consequently, under natural conditions also) apparent muscular exhaustion is often due to the fact that the nerve spike becomes subthreshold as fatigue develops in the muscle. Unless the muscle is completely unfatigued, it is impermissible to use muscular response as an index to excitation of the nerve.

A description is given of a new type of stimulating and test electrodes for the nerve, used in these experiments, and the significance of the findings is discussed.

DUYFF, J. W. (Leyden). Experiments on muscular fatigue, with special reference to the Scheminzy-effect.

A report is given on experiments made on the Scheminzy-effect. The gastrocnemius muscle of the common frog (*R. esculenta*) was used, and fatigue was brought about by tetanic stimulation with induction shocks furnished by a rotating interruptor. An analysis of the phenomena of fatigue is given, and the concept of relative fatigue is discussed. It is shown that, contrary to *Scheminzy's* opinion, the effect of a reversal of the current is largely due to the fact that fibres which had ceased to respond prior to the reversal are again thrown in action, and that the changes responsible for the development of relative fatigue are probably not confined to the cathodal region, but that conditions at the anode are also of importance in this respect.

The results obtained are consistent with the view that quick, easily fatigued fibres, having a high intensity threshold and a low time constant, are relatively more numerous at the distal extremity of the muscle while slower fibres, which are less easily fatigued, and which have a lower intensity threshold, but a higher time constant, prevail in its proximal part. The relation of these findings to the results of *Sommerkamp*, *Wachholder*, and others, and the physiological significance of the differences in excitability between the two fibre types are discussed.

FELDBERG, W., and HEBB, CATHERINE O. (Cambridge). The stimulating action of phosphates on the superior cervical ganglion of the cat.

Experiments have been performed on chloralosed cats to examine the effects of adenosine triphosphate (ATP) and creatine phosphate (CrP) on the perfused superior cervical ganglion using contraction of the nictitating membrane as an index of stimulation. The experiments were undertaken because: (1) ATP and certain other phosphates cause contraction of skeletal and smooth muscles (*Buchthal, Deutsch, and Knappeis*, 1944; *Buchthal and Folkow*, 1944; and *Buchthal and Kahlson*, 1944, 1946). (2) ATP and CrP may each take part in the synthesis of acetylcholine (*Nachmansohn and Machado*, 1943; *Feldberg and Mann*, 1945; *Feldberg and Hebb*, 1946; and *Torda and Wolff*, 1946).

Both ATP and CrP have been found to stimulate the sympathetic ganglion. The effect is not dependent on either the release of acetylcholine or on its synthesis, because it can equally well be demonstrated on the chronically denervated ganglion (section of cervical sympathetic eight days before experiment) which contains little or no formed acetylcholine and is unable to synthesize it. The stimulating action of the two compounds is due to their phosphate content since adenosine and creatine do not elicit any response. In this connexion no special significance is to be attached to the fact that the phosphate of ATP and CrP is present in a highly labile form. Equally strong stimulation of the ganglion can be obtained with other more stable phosphate compounds such as muscle and yeast adenylic acid, sodium triphosphate, pyrophosphate, and orthophosphate.

The stimulating effect of acetylcholine on the ganglion may be distinguished from the stimulating effect of potassium or of citrate by the fact that its action is prevented both by curare and by high concentrations of eserine, while in the case of the other two substances curare does not affect the response, but it is abolished by eserine. Similarly the action of the phosphate compounds is not prevented by curare, and therefore differs from that of acetylcholine, but is prevented by eserine and so is analogous to the action of potassium or citrate. In this connexion it may be men-

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tioned that the eserine paralysis is independent of the acetylcholine metabolism of the ganglion since it is demonstrable in the chronically denervated ganglion.

Buchthal, F., Deutsch, A., and Knappeis, G. G., *Acta Physiol. Scand.* **8**, 271 (1944). Buchthal, F., and Folkow, B., *Acta Physiol. Scand.* **8**, 312 (1944). Buchthal, F., and Kahlson, G., *Acta Physiol. Scand.* **8**, 317; **11**, 284 (1944, 1946). Feldberg, W., and Mann, T., *J. Physiol.* **104**, 8, 411 (1945). Feldberg, W., and Hebb, C. O., *J. Physiol.* **105**, 8 P. (1946). Nachmansohn, D., and Machado, A. L., *J. Neurophysiol.* **6**, 397 (1943). Torda, C., and Wolff, H. G., *J. Biol. Chem.* **162**, 149 (1946).

GAARENSTROOM, J. H., and DE JONGH, S. E. (Leyden). Growth in hypophysectomized rats treated with alloxan.

Several reports of the past years suggest a connexion between the actions of the pituitary growth hormone and of insulin (Marx, C. S.,¹ Gaebler and Abner²). In view of this we investigated if the effect of growth hormone on growth was impaired by damaging the pancreatic islets through treatment with alloxan. Experiments were carried out on rats (bodyweight 156–212 gm.) which received a single injection of alloxan (15–20 mg./kg.) and were hypophysectomized either on the same day or three days later. Treatment with 20 µg. daily of a partially purified growth hormone preparation was instituted the day after the operation and was continued for 6–15 days. In groups of control animals either the administration of alloxan or of growth hormone was omitted.

Of 22 rats, hypophysectomized and injected with alloxan on the same day, 9 were treated with growth hormone. The average bodyweight decreased to 97% during the first three days of the treatment but thereafter increased to 113% on the fifteenth day. In the 5 animals which were treated similarly except for the alloxan injection these data were 93% and 112%. The bodyweight of 8 hypophysectomized alloxan-treated animals which received no growth hormone decreased to 80% during the 15 day period. The weight of several organs was compared with their initial value by means of a fourth group of animals killed at the beginning of the experiment. The weight of the M. gastrocnemius rose 22%, of the tibia 19% after treatment with growth hormone, and the weight of the kidney decreased by 5%. This exceptional behaviour of the kidney (and liver) was

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already observed by us in earlier experiments in which no alloxan was given.

Except for two rats (in the growth hormone group) none of the alloxan animals excreted sugar. From earlier experiments we knew this as a common feature in hypophysectomized rats injected with alloxan, regardless of the damage done to the islets. On the contrary we observed that the effect of alloxan to the islets is more severe in hypophysectomized animals than in normal ones.

Nevertheless in a second group of rats alloxan was administered three days before the ablation of the hypophysis and during this period the excretion of sugar was determined. Only the animals which excreted (the very large amount of) 3 gm. glucose or more a day were included in the groups. After the hypophysectomy the 10 animals which received growth hormone showed a bodyweight increase of 10% in 9 days and 18% in 15 days. The animals which were not treated with growth hormone decreased 10% in 9 days and 21% in 15 days. Sugar excretion soon fell to 1 gm. a day on the average after the operation.

In two smaller rats injected with alloxan which excreted 4.7 and 6.2 gm. a day respectively and continued to do so after hypophysectomy, bodyweight increased by 42% in 6 days after treatment with growth hormone.

From these results it may be concluded that the increase in weight of the body and of the separate organs which follows the treatment with growth hormone is not affected by the functional ablation of the pancreatic islets with alloxan.

¹ *Am. Journ. Physiol.* 141, 88 (1944).

² *Endocrinology*, 30, 627 (1942).

GARCIA-BLANCO, J. (Valencia, Spain). **Some peroxidasic methods for the demonstration of intracellular haemoglobin.**

The foundations for several histochemical methods are explained that permit the intracellular staining of the haemoglobin in an intensity proportional to its concentration in the cell. All of them are based on the haemoglobinic peroxidation of a substratum bringing out different colours. The conformity of the results obtained by different methods, and the great sensitivity of some of them, suggest their eventual application to the study of haemogenesis and haemocathesis.

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1. The 2-6-dichlorophenol-indophenol discoloured by ascorbic acid rapidly takes, at pH 7, a blue colour in the presence of hydrogen peroxide and haemoglobin.

Bathing a smear of blood or bone-marrow with a solution concentrated in methanol of 2-6-dichlorophenol-indophenol discoloured by ascorbic acid, and then washing with another alcoholic solution of hydrogen peroxide at pH 7.5, the cytoplasm possessing haemoglobin take a beautiful blue colour.

2. The para-diaminodiphenylamine takes in the presence of hydrogen peroxide and haemoglobin an intense blue colour turning on red at pH above 8.

Bathing a smear of bone-marrow with a methanolic solution of para-diaminodiphenylamine containing hydrogen peroxide, a brownish red coloration of the cytoplasmic haemoglobin and of certain intranuclear structures and blue of the nuclear plasma is obtained.

3. Para-phenylenediamine in methanolic solution tinges the haemoglobin plasma, in the presence of hydrogen peroxide, with diverse colours according to the substance added to the system:

(a) Chestnut colour with catechol.

(b) Violet with naphthol alpha.

(c) With orthoaminobenzoic acid the tincture is the same as the one described for para-diaminodiphenylamine.

4. Benzidine in methanolic solution with H_2O_2 tinges the haemoglobin cytoplasm and certain nuclear structures of the red cells an intense blue colour if one adds to the system some of the aminobenzoic acids, and a red colour if tannic acid or glycocholic is added.

5. Some of the aforementioned methods, moreover, tinge the oxidizing and peroxidizing granulations of the leucocytes.

6. Most of the methods indicated permit of contrasting colorations with the specific tint of the nucleus.

HELLER, C. G., and NELSON, W. O. (Oregon, Iowa). Evidence that chorionic-gonadotrophic-hormone stimulates Leydig-cells to produce androgen and that follicle-stimulating hormone stimulates spermatogenesis in man.

Twenty-two hypogonadotrophic eunuchoids ranging in age from 18 to 56 years of age served as subjects. To qualify for admission to

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this heretofore unrecognized syndrome the following criteria were used: (1) eunuchoidism associated with sexual infantilism, (2) urinary gonadotrophic titers below range for normal men, (3) Leydig-cells undeveloped, (4) seminiferous tubules undeveloped, (5) low urinary 17-ketosteroids, (6) low urinary estrogens, (7) absence of gynecomastia.

Testicular biopsies were performed before and after treatment with chorionic gonadotrophins, and after treatment with a purified follicle stimulating hormone. Assays of urinary gonadotrophins, 17-ketosteroids and estrogens were performed before and during treatment.

That chorionic gonadotrophin administration (1,000-1,500 international units intramuscularly daily or 750 I.U. twice daily) caused endogenous androgen secretion was adduced from: (1) skeletal, somatic, and sexual maturation; (2) elevation in 17-ketosteroid and estrogen secretion.

That the androgen was produced by Leydig-cells is adduced from the change in microscopic appearance of the cells, i.e. from immature to entirely normal, and from the fact that eunuchoids without testes failed to respond to similar treatment.

No germinal maturation was noted in the biopsies nor were spermatozoa found in the seminal emissions obtainable during chorionic gonadotrophin administration. Following daily administration of follicle-stimulating hormone (while continuing chorionic gonadotrophin injections) spermatozoa appeared in the seminal fluid and testicular biopsies revealed normal spermatogenesis in all five patients examined.

HELLER, JÓZEF (Wrocław, Poland). Metabolism of insect metamorphosis.¹

Chrysalids of the Hawk-moth (*Celerio euphorbiae*) immediately after pupation and then successively during hibernation and the development period were ground with sand and with 9-fold amount of 1/15 M. phosphate buffer (pH 6.2). In 1 ml. of the brei oxygen consumption was estimated in the Warburg-apparatus at 18° C. during three hours or more.

1. Respiration during the whole pupal stage proved to be in the

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brei as high as in the intact pupa, i.e. falling from ca. 300 ml. per kg./hour in fresh pupa to 20–30 ml. during hibernation and then rising during the development period to reach the initial level. These remarkable changes cannot be correlated with the amount of tissue formed, as was admitted by A. Krogh and others. *They are not structure-bound, but conditioned by humoral factors.*

2. It could be inferred from the former work of the author² that the regulating mechanism of the respiration consists in inactivation of coenzymes due to dephosphorylation. In the present investigation a cozymaze preparation or boiled yeast-extract was added to the brei. As a result a rising of oxygen intake, prolonged duration of the respiratory activity, and retardation of the blackening of the brei was observed. This blackening (formation of melanin) was always noticed toward the end of the respiratory activity of the sample. If fresh cozymaze is added in this moment, the colour fades. From the above it is inferred *that cozymaze is the main hydrogen acceptor from metabolites and that the tyrosinase-tyrosine system is concerned with further transport and oxydation of this hydrogen.*

3. At pH 7.0 all respiration of the brei is stopped. Above and below this point the oxygen consumption rises. Thus pH 7.0 seems to be the isoelectrical point of some essential catalyst.

4. The addition of the Lebedew yeast-juice to the brei of hibernating chrysalids causes immediately a rapid ca. tenfold rise of oxygen consumption which lasts for about 90 minutes. Then it drops abruptly and melanin is rapidly formed. Poisoning with 1/20,000 M. KCN increases the oxygen intake in these experiments about 50%. These findings are interpreted as a competition for the hydrogen of dihydrocozymaze between the physiological partner—i.e. tyrosinase with dopa and its quinone (or hallachrome and its reduced form) on the one side and the flavoproteine (the yellow enzyme) of yeasts. The last—being more effective—dehydrogenates not only all dihydrocozymaze present, but also the quinone system, forming the melanotic pigment.

The augmentation of oxygen intake in KCN poisoned brei can be accounted for as inhibition of catalase. The resistance of respiration to KCN makes it unlikely that the Warburg-Keilin system may play any role in this period of pupal life.

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Thus the physiological role of tyrosinase in insect metamorphosis as terminal link in the respiratory system of chrysalids seems to be established.

¹ The author is indebted to Prof. Parnas for the opportunity of performing this investigation in 1940-1. A preliminary report was given in a meeting of the Physiological Society in Lwow, April 1941. ² *Biochem. Z.* 219, 473 (1930) and *C.R. Soc. Biol.* 121, 414 (1936).

HUBLÉ, J. H. and GAARENSTROOM, J. H. (Leyden). Sugar tolerance in hypophysectomized rats.

If hypophysectomized rats are pretreated with alloxan (one injection 3 days before the operation), the subsequent diabetes is less pronounced than in rats to which alloxan is given on or after the day of hypophysectomy. Since the sugar excretion is an unsuitable test in this connexion, this observation was based on determinations of the blood sugar level after glucose administration (3 ml. glucose 20% per os. and 2 ml. intraperitoneally). This suggested a less severe damage of the islets of Langerhans in non-hypophysectomized rats or a partial recovery during the three day period between alloxan administration and hypophysectomy (*Gaarenstroom et al.*).¹

From this the possible existence of a pancræotropic effect exerted by the hypophysis might be concluded. If so, a decrease in the insulin production would be expected after hypophysectomy (in animals not treated with alloxan). We determined therefore the blood sugar level before and after sugar administration in fasted albino rats hypophysectomized 3-6 weeks previously. The fasting blood sugar levels were not markedly changed compared with the corresponding values of normal control rats, but the level after sugar administration showed a considerable increase. Average of 27 rats 317 mg.% (32 normal controls 129 mg.%).

If hypophysectomized rats are treated from the day of operation with a pituitary extract with strong growth stimulating properties (20 μ daily) the increase of the blood sugar level does not appear (6 rats av. 100 mg.%).

In a few experiments with hypophysectomized rats of a coloured strain the same lowering effect of the treatment with the extract was observed, though the level of the non-injected animals was much lower.

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The extract was not a highly purified one, therefore other anterior lobe hormones than growth hormone might have contributed to the effects observed. For instance a high blood sugar level was found after sugar administration in thyreodectomized rats (av. in 6 rats 291 mg.%). The increase after hypophysectomy might be explained therefore by the atrophy of the thyroid gland which follows the ablation of the hypophysis. However, the extract prevented the rise of the blood sugar level not only in hypophysectomized rats but in thyreodectomized rats as well (5 rats av. 158 mg.%). In addition it was known to us from other experiments that the thyrotropic activity of the preparation in the dose used was negligible.

An investigation for possible histological changes in the pancreatic islets is not yet completed.

It can be concluded that a given amount of sugar is more easily metabolized in the presence than in the absence of the pituitary gland. This hypophyseal effect can be restored by a not highly purified growth hormone preparation. The assumption that this influence (which perhaps is a pancretotropic one) may be ascribed to the growth hormone is attractive in connexion with the present views on this subject.

¹ *Acta Brev. Néerl.* 14, 70 (1946).

HURYNOWICZ, JANINA (Toruń, Poland). **La chronaxie des réflexes vestibulaires dans le sommeil narcotique.**

Les recherches en question ont été exécutées au Laboratoire de Physiologie Générale de l'Université S. Batory à Wilno en 1938-9 sur des lapins. On appliquait à doses différentes intraveineuses, sous-cutanées, per rectum les substances somnifères et narcotiques comme: hydrate de chloral, chloralose, avertine, urétane, NaBr, MgSO₄, dites corticales, et celles portant sur des régions sous-thalamiques et du tronc cérébral: médinal, scopolamine, pantopon.

On observait l'état, le comportement de l'animal durant plusieurs heures (jours) et on mesurait toutes les 30' les chronaxies des trois réflexes vestibulaires (la déviation de l'œil-chronaxie probablement sacculaire, l'inclinaison latérale de la tête — chronaxie utriculaire, et le nystagmus lié à la fonction des canaux semicirculaires). Les

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chronaxies normales de ces réflexes furent déterminées par l'auteur en 1935.

Les résultats de nos expériences ont démontré que, outre les signes classiques de la narcose et du sommeil dans le domaine des manifestations corticaux et sous-corticaux, on observe chez l'animal au début, pendant et après le sommeil, provoqué par les agents mentionnés, des troubles végétatifs, anaphylactiques (ressemblant au choc), myotatiques et myotoniques.

L'excitabilité chronaxique des trois réflexes labyrinthiques nommés donne des modifications bien nettes et déterminées.

Les différences de caractère, d'intensité de tous ces phénomènes dépendaient de la particularité de l'agent administré, de la voie d'introduction et de la dose appliquée.

Le tableau ci-dessous illustre les résultats globaux des changements des chronaxies.

L'excitabilité chronaxique

	<i>I. La Déviation de l'œil</i>	<i>II. L'Inclinaison de la tête</i>	<i>III. Le Nystagmus</i>
<i>Agents dits corticaux:</i>			
Hydrate de chloral	augmentée	diminuée	augmentée
Chloralose	augmentée	diminuée	augmentée
Avertine	diminuée	augmentée	diminuée
NaBr.			
„ (doses moyennes)	diminuée		
„ (doses élevées)	augmentée	diminuée	augmentée
Urétane	augmentée	augmentée	
<i>Agents dits sous-thalamiques et du tronc cérébral:</i>			
Scopolamine }	diminuée	diminuée	augmentée
Pantopon }		diminuée	
Médinal }		augmentée	diminuée

Conclusions:

I. L'appareil vestibulaire chez le lapin par ces trois réflexes:

I. la déviation de l'œil,

II. l'inclinaison de la tête,

III. le nystagmus

est en rapport bien proche avec les fonctions du système nerveux végétatif et entre dans l'orbite des phénomènes du sommeil et de la

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narcose, durant lesquels il subit des modifications d'excitabilité chronaxique.

2. Les résultats des recherches dans la narcose et le sommeil provoqués par l'administration des différentes substances narcotiques et somnifères dites corticales et sous-corticales prouvent que non seulement chacun de ces réflexes vestibulaires a son arc réflexe spécial, ainsi que le champ et le centre cortical précis, individuel et propre à lui, mais que chacun de ces mécanismes est bien indépendant dans ses fonctions, voies et centres des connections et que la narcose et le sommeil portant probablement sur des centres de coordination et subordination provoquent cette variabilité des phénomènes observée dans ces cas.

3. Les substances narcotiques utilisées ont, il paraît, une action bien réglée et déterminée dans leur influence sur les différentes régions du système nerveux.

KLISIECKI, A. (Wrocław, Poland). The action of shock-producing substances upon the heart (histamine, adenylic acid ADL, adenosine-3-phosphoric acid ATP, peptone, acetylcholine, blood-serum).

It has been shown that histamine-shocks are induced by inhibition of the heart (Klisiecki and Holobut, *Arch. Exp. Path. Pharm.*, 1937).

Intravenous injection of 0.25–0.5 mg./kg. ATP increases the coronary circulation in dogs (11–70%), decreases pulse-rate (16–28%) and arterial pressure (8–20%). Greater amounts (1.5–5 mg./kg.) also increase the coronary flow, but reduce the pulse-rate to 70–20% and arterial pressure to 40–25% of the normal. Convulsions of the body and respiratory changes soon appear in these circulatory disorders; profound shocks lasting several minutes appear, all ending in recovery. Even 70 mg. of ATP injected during several hours do not paralyse the heart.

ADL 0.1–0.25 mg./kg. induces transient fall of pressure with increase of coronary flow. Greater amounts (0.4–0.8) are dangerous to the general circulation because of reduction of pressure to 50–60% of the normal (Klisiecki and Zalucki, 1939, not published).

To trace the influence of these substances upon the general circulation, the blood flow in arteries of the rabbit was measured. The

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flow diminished progressively with the fall of arterial pressure, returned to normal with the recovery of the heart, and was much greater for some time because of vasodilatation.

Infusion of ATP and ADL-solution (into proximal end of abdominal vein of the frog, while the outflow from the peripheral end of this vessel was recorded) showed that the outflow was greatly reduced, and respiration came to a standstill in the period of the heart-disorder. Only with the recovery of the heart abundant outflow appeared. But when the solution was infused into the aorta (leaving the heart to one side), there was continuous augmented outflow, depending on the pressure of the solution.

Acetylcholine gave similar results upon heart-work and blood-circulation.

The conclusion should be drawn from these experiments that the action of vasodilating substances and therapeutic doses should be investigated on the whole animal, not on isolated organs. As far as is known all vasodilating substances inhibit the heart-work.

In 1941 the cause of heterogenic shock was investigated (*Klisiecki* and *Fedorof*). Two c.c. of rabbit-blood were intravenously injected into dogs; blood-flow in arteries, vena portae, and pulmonary artery was recorded. The flow in arteries diminished parallel with the fall of blood-pressure, and no bleeding into peripheral vessels was observed. In pulmonary artery and vena portae no trace of vasoconstriction was to be noted. Shocks were manifestly induced by the circulatory disorders located in the heart. The same was observed after injection of peptone.

Though there are numerous causes of dying, there is lastly only one manner of extinction of life, i.e. the cessation of the heart-beat. Prolonged dying is induced by various natural causes, infections, neoplasms, and so on; sudden death by quickly acting harmful agents, i.e. by shock-producing substances (chemicals, burns, bleeding, electric current and stimuli which weaken the heart by the nervous reflex action).

KONORSKI, J. (Lodz, Poland). On the summation of the conditioned reflexes.

As homogeneous conditioned reflexes (i.e. reflexes reinforced by the

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same unconditioned agent) can be considered as a particular case of allied reflexes it is to be expected that the principles of their summation should conform to the general principles of reflex summation laid down by *Sherrington* and his associates.

Indeed, as *Pavlov's* co-workers (*Rikman*, *Galperin*, *Zevald*, and others) have demonstrated, the summation of two conditioned reflexes, one of which has a maximal value, results in a response *which does not exceed the effect of the strong stimulus. Taking into account that both conditioned reflex-arcs in question converge upon one and the same 'unconditioned centre' one has no difficulty in explaining this fact as due to occlusion.*

The present paper deals with the problem of the summation of very weak conditioned reflexes. To obtain such reflexes the continuous (and not rhythmic as usually) light tactile stimulation of the dog's skin and the very weak visual stimulus were used. These stimuli were reinforced by food. We found that the summation of such reflexes results in their considerable facilitation, owing to which the response to both conditioned stimuli applied in association greatly exceeds the sum of their separate effects. In one or two experiments by diminishing the dog's alimentary excitability (the dog was fed before the experiment), we succeeded in obtaining an exceedingly small (almost zero) effect to each stimulus; nevertheless the reflex to their joint application was quite appreciable.

The study of the summation of weak conditioned reflexes is complicated by the fact that they are usually very irregular in size. The same was observed by *Cooper*, *Denny Brown*, and *Sherrington* in regard to very weak spinal reflexes.

The following conclusions can be drawn from these data: (1) The laws of the summation of conditioned reflexes are exactly the same as those of the summation of innate reflexes, displaying both occlusion and facilitation. (2) The results obtained suggest that in very weak conditioned reflexes impulses set up by the 'conditioned centre' and reaching the 'unconditioned centre' are unable to excite all neurons of this centre supraliminally, leaving some neurones in the state of the subliminal fringe. In some cases the conditioned reflex can even be totally subliminal. (3) It is suggested that the interaction between the excitatory and inhibitory conditioned reflexes could be analysed and explained in the same way without referring to the

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Pavlovian laws of irradiation and concentration and mutual induction of cortical processes.

LUNDBERG, N. ERIK (Stockholm). **Acidosis following on insulin treatment.**

Ever since insulin came into use we have been confronted with the inconvenience of the small glycogenous deposits that are common in diabetics who have been treated with insulin. They appear in the form of hypoglycemic symptoms after (even fairly small) doses of insulin, particularly in connexion with muscular exertion.

Acidosis follows on reduced or insufficient carbohydrate consumption and increases in diabetics who show a failing capacity to absorb insulin. Its appearance is looked upon as being a sure sign of a lack of insulin in the case of carbohydrate insufficiency.

Such is not the case, however. If a diabetic, who is otherwise well adjusted (balanced) as regards insulin treatment, gets his glycogenous deposits emptied and his blood sugar drops to 50 mg.% or lower, acidosis may be the result. This is not due to *too little* but to *too much* insulin as compared with the carbohydrate reserve. It is all the more striking if we compare the insulin tolerance of diabetics with that of (metabolically) healthy schizophrenics, who must be given insulin doses of 300-400 I.E. and more in order to bring about a shock effect.

The phenomenon has nothing to do with rhythm, it can be produced at any time by means of muscular exertion. Therefore when treating diabetics it is extremely important to build up a sufficient reserve of glycogen.

MISSIURO, W. J. (Łódź, Poland). **The effects of ultra-violet radiation on rabbits with reference to factors determining their resistance to anoxia and high altitude.**

Current studies on the action of ultra-violet radiation on living organisms and especially the indications of its beneficial effect on haemopoietic function gave us some reason to believe that U.V. radiation, by leading to the rise of blood Hb level, might for this reason alone increase the resistance of animals to the anoxia under conditions of decompression.

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The first stage of investigation, started in the Department of Physiology, Edinburgh University, was to find conditions such as would ensure this beneficial response, assessed chiefly on the haemopoietic effect of U.V. treatment.

The experiments were performed on 66 rabbits, approximately half of which were subjected to U.V. treatment. The animals were arranged in 8 groups, irradiated and control animals. Hanovia U.V. lamp was used. The intensity of exposure was kept constant in all groups; but the duration of exposure (progressive as well as rapid increase of daily dose up to 60 min. and even 120 min. were used), and total period of treatment were varied for different groups from 5 to 14 days.

Height-resistance tests have been carried out in decompressions accomplished in 5-7 min. to pressures approximately equivalent to 34,000 ft. (210 and 195 mm. Hg). During and subsequent to decompression, the animals breathed air constantly circulated through the chamber.

The blood response produced by radiant energy was typically diphasic and shown to a greater or lesser degree by all groups of animals treated.

First phase, associated with the beginning of treatment period, was characterized by a tendency to intravital haemolysis, decrease in red cell count, lowering of blood Hb (determined by cyan-Hb method of *Stadie and Wu*) and haematocrit values. Reticulocytosis may intervene during this phase.

Second phase was regenerative in character and coincided with the post-irradiation period up to 25 days in some cases. It was characterized by a mounting reticulocyte count and a gradual rise in red cell count, haemoglobin and haematocrit values to levels which may equal or exceed the original levels.

The net result of these changes was two-fold: a fairly marked increase in haemoglobin of originally anaemic animals; and an increase in the average corpuscular Hb value (%) presumably because of the relative preponderance of young red blood corpuscles. This second effect persisted for some days at least after recession of reticulocytosis, e.g. during the third week of the post-irradiation period.

Increase in the daily dose of radiant energy led generally to more uniform blood response, but unfortunately in some cases it gave rise

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to serious pathological changes in the liver. Post-mortem histological examination of animals so treated and subsequently dying from decompression showed appearance of areas of lobular necrosis with disappearance of nuclei, granulations but no leucocytic infiltration.

The number of animals tested in the decompression chamber is small (34 pre-treated and 32 control) and the mortality rate of pre-treated animals as compared with the controls is not significantly different. However, the animals which tended to survive were those in which irradiation produced a rise in the Hb/haematocrit ratio. It has also been found that pre-treated animals died in decompression in most cases later than the controls.

NIEMIERKO, W. (Łódź, Poland). *Metabolism of the bee-moth larvae (Galleria mellonella).*

1. *Chemical composition of growing larvae.* Larvae of different sizes from 10 to 200–250 mg., i.e. towards the end of larval life, were analysed and the following body constituents determined: dry substance, lipids, saturated and unsaturated fatty acids, iodine and rhodan numbers, nitrogen, glycogen, chitin, and ash content. The most significant chemical changes during growth are connected with lipids accumulation; fatty acid content increases from 18 to 43% of dry substance (saturated acids from 7 to 14%, unsaturated from 11 to 29%); simultaneously protein and ash content decreases. Residual constituents do not exhibit distinct changes.

2. *Utilization of wax constituents by larvae.* Small larvae (about 10 mg. each) were kept at 30° C. during 10 to 15 days till all the wax put into the vessel was consumed. Excreta and larvae (weighing then about 100 mg. each) were analysed separately and the balance for water, lipids, and residual substances was calculated. The formation of 1 mg. of body lipids is connected with consumption of about 13 mg. of wax lipids; 6 mg. of them are oxidized and 7 mg. excreted. Fatty acids and unsaponifiable matter are utilized unequally: 14% of consumed fatty acids are retained in the larval body, 43% oxidized, the same amount being excreted; not more than 2% of unsaponifiable matters are retained, 47% excreted, and 53% metabolized. Since the last substances are the chief constituents of wax (60%), the results obtained here show that bee-moth larvae

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utilize much more of them (twice) than of fatty acids. Besides, it seems that a part of unsaponifiable matter is converted into fatty acids. Fatty acids of larval body have a higher acid number than those of wax (195 and 162 respectively), which means that a shortening of the carbon linkage takes place during fatty acid accumulation by larvae.

3. *Metabolism during starvation of larvae.* Larvae were deprived of food and the chemical composition of their body was determined during various periods of starvation. It was found that large amounts of lipids were metabolized whereas only insignificant amounts of other substances disappeared. At the beginning of fasting unsaponifiable matters are utilized in the first instance, in a few days they are nearly exhausted; in agreement with the results mentioned in (2) there is some evidence that unsaponifiable matters can be transformed into fatty acids. The unsaturated acids are oxidized in larger amounts than the saturated. Concluding from the amount of lipids which disappear the metabolic rate is very great. In one of the experiments during 8 days of starvation more than 200 mg. of lipids calculated for 1 gm. of dry body substance (nearly one-half of their content) were found oxidized.

PAPPENHEIMER, J. R., and SOTO-RIVERA, A. (Boston). **The effective osmotic pressure of the plasma proteins and other quantities associated with the capillary circulation in mammals.**

Factors determining the passage of fluid across the capillary wall include the capillary pressure, the effective osmotic pressure of the plasma proteins and the filtration constants of the capillaries themselves. We are now able to measure all three of these quantities with an accuracy of approximately 5% in isolated perfused hindlimbs of cats and dogs.

The limbs are suspended on a sensitive recording balance and are provided with heparinized blood from a pump-lung circulation. The rate of fluid movement is determined from the rate of change of weight. For any given protein concentration, there exist an infinite number of pairs of values of arterial and venous pressures (pA , pV) at which the leg neither gains nor loses weight. Under these condi-

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tions the mean capillary pressure (pC) is equal to the sum of all pressures opposing filtration. This we call the isogravimetric capillary pressure ($p\bar{C}_1$). Its value is determined with an accuracy of ± 1.0 mm. Hg as follows: pA and pV are simultaneously varied in opposite directions by amounts such that $p\bar{C}_1$ remains constant as evidenced by constant weight. As $pA - pV \rightarrow 0$, each must approach $p\bar{C}_1$. When $pA - pV$ is plotted against pV (isogravimetric values) the intercept on the pV axis is then $p\bar{C}_1$. In practice it is more convenient to plot the isogravimetric blood flow against pV and extrapolate to zero flow. This relation is linear whereas $pA - pV$ vs. pV is alinear owing to anomalous viscous flow in the arterioles. When most of the corpuscles are removed both methods may be employed with equal accuracy.

The isogravimetric capillary pressure so calculated is $95 \pm 5\%$ of the osmotic pressure of the plasma proteins as determined in an osmometer *in vitro*. This is true over a range of protein pressures (8–30 mm. Hg) obtained by concentrating the plasma. (Crystalline protein fractions are also being investigated.) The largest source of error in the comparison is believed to be the *in vitro* measurement of osmotic pressure.

The slope of the line relating isogravimetric venous pressure to blood flow is the resistance to flow from the effective mid-point of the capillaries to the vein. Knowing this value, the mean capillary pressure at any other (non-isogravimetric) value may be computed from the resistance and the flow. The difference between the capillary pressure so calculated and the isogravimetric capillary pressure is the pressure-head available for filtration. The rate of filtration or absorption is found to be accurately proportional to this pressure-head which has been varied over the range -15 to $+20$ mm. Hg by changing arterial, venous, and protein pressures. The average proportionality constant in 13 hindlimbs was 0.011 ± 0.001 (S.D. ± 0.003) c.c. per minute per mm. Hg pressure gradient across the capillary wall per 100 c.c. of leg tissue.

Since the arterial, venous, and capillary pressures are known, the resistance to flow of both sides of the capillary circulation may be quantitatively studied.

RUCH, T. C., CHANG, H. T., and WARD, A. A., Jr. (Seattle and New Haven). **Topographical vs. functional organization of the motor cortex of the monkey.**

The possibility that muscles as well as movements are represented in the motor cortex has been investigated in macaque monkeys by a polymyographic technique. The responses of individual muscles to cortical stimulation were recorded simultaneously by eight isometric myographs inscribing on two long-paper kymographs. A Sherrington preparation of all the muscles acting over the ankle was made by appropriate dissection of the tendons and nerves of the leg. The free surface of the leg area was mapped on cellophane and explored and re-explored, millimeter by millimeter, using a unipolar electrode and a Goodwin thyatron stimulator. Light Dial was used for anaesthesia.

The polymyographic technique affords a quantitative demonstration of certain classic observations on the degree to which various classes of muscles are represented in the cortex. The tension per gram of muscle weight of responses induced from the free surface of the leg area is many times greater in distal muscles than in proximal ones, and in anatomical extensors than in anatomical flexors.

The polymyographic technique provides direct evidence of the responses of individual muscles to cortical stimulation. For several of the muscles under observation, a focal point of representation was identified from which responses in a single muscle were elicitable by near threshold stimulation (*solitary responses*). When more than one muscle responded to the stimulation of a cortical point, the topographical differentiation of cortical points for different muscles was nevertheless demonstrable by comparing the relative strength and latency of their contractions. When the latencies or tension ratios are plotted for each cortical point, a meaningful topographical pattern emerges. It is concluded that each ankle muscle is represented by a field composed of a focus and a fringe, the degree of representation decreasing in passing from the focus to the periphery of the fringe. There is considerable overlapping of the representation of different ankle muscles. However, re-representation of muscles (i.e. multiple focus-fringe pattern) was not encountered. It is postulated that the focus-fringe pattern is characteristic of the Betz cell layer and that movement patterns are organized by intracortical

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neurons. Though the motor cortex organizes simple movements, it does so by employing a topographically organized substrate.

SCHILD, H. O., and GREGORY, R. A. (London and Liverpool).

Liberation of histamine from striated muscle by curarine, strychnine, and related substances.

Arising out of the demonstration by *Alem, et al.* (*J. Physiol.*, 1940) that curare causes the release of histamine activity from isolated perfused striated muscle, a study has been made of the release of histamine activity from striated muscle preparations by d-tubocurarine chloride, strychnine methiodide, strychnine nitrate, and methyl-bebeerine. Experiments were made on either the isolated tongue or isolated blood-perfused hindlimbs of the dog, using heparinized or defibrinated blood. All these substances were found to release histamine activity as evidenced by increased venous flow, a fall in perfusion-pressure and the pressure of histamine activity in venous samples extracted by *Code's* method. Although d-tubocurarine chloride caused the greatest release of histamine activity of the substances tested, no close correlation was found between curariform action and the power to release histamine activity. The histamine-like substance appeared to be released in a free and active form, as shown by the following findings: (a) vasodilatation occurred and was related in degree to the blood histamine activity found after extraction, (b) more of the histamine-like substance released was present in the plasma than in the corpuscles, and (c) assays of untreated plasma on guinea-pig ileum and cat's blood pressure agreed closely with assays of the same plasma after extraction.

SZABUNIEWICZ, B. (Krakow, Poland). **Electric phenomena in muscle contracture.**

Action potentials of frog muscles were recorded with a string galvanometer. One electrode rested on the muscle, the other being earthed. Several records from the same muscle, every 2 mm. along its fibres, were obtained. Simplest results were obtained on *gastrocnemius*, *peroneus*, *tibialis posticus*, and *tibialis anticus*.

With indirect excitement, potential changes commenced 4 msec. after stimulation, simultaneously on the whole surface of the muscle.

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Every record shows a diphasic current, the top of the first phase happening 12.2 msec., the second phase 24.2 msec. after stimulation. Both phases occurred simultaneously in the whole muscle. The potential changes of a muscle were measured on the curves of action potential.

The reaction can be divided in two phases: in the first there is a 'descendent' polarization of the muscle surface, in the second a polarization of the same size in the opposite, ascendent, direction. These changes are not easily explained with the depolarization of the muscle membranes. This could be done much more easily with the assumption of a lengthwise dislocation of muscle ions.

The electric phenomena of the 'action current' can be made durable. Durable potential changes, adequate to the first phase, may be obtained by sectioning the muscle along its fibres with a very sharp razor-blade. The potential then rises in the direction of the peripheral end. Differences of 30 mV. between the ends of the muscle may be noted. The phenomena are equally marked on the wounded and unwounded muscle surface.

Durable polarization, adequate to the second phase of 'action current', arises under the influence of many agents, e.g. warming for several seconds at 45°, contact with skin secretion of the frog, or many chemicals. In these conditions the muscle reacts with *polarization contracture*: it contracts by 20–25% of its length and shows a gradual fall of the potential along the fibres to the periphery. Differences of 70–80 mV. can be noted. The changes stay for hours. Polarized muscles contract under nerve stimulation, but their reaction is lower by the height of the polarization contracture. Their action current shows the first phase of changes only.

Phenomena described above are to be explained only by assumption of electric asymmetry along muscle fibres.

UYLDERT, INA E. (Amsterdam). **Progestational phenomena in the rat.**

In pregnancy the type of endocrine integration is progestational. Characteristics of gestation are in the ovary: large pregnancy corpora lutea, persisting longer than those of the cycle. In the uterus: a deeply indented structure with prevalently epithelial character. In

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the vagina: multilayered mucified epithelium supplanting the estrous or diestrous types of the cycle. In the mamma: galactophores with extensive budding and arborisation yielding up to 10 gm. tissue. In addition to natural pregnancy the progestational (gestational) condition can be artificially obtained in the presence or even in the absence of the ovary.

Estrogens combined with progestational steroids whose protagonist is progesterone produce the gestational condition in the accessories. In addition to substitutional modes of treatment a more baffling response is that obtained in normal adult rats with ultra-physiological doses of estrogens alone. In 10-20 days a complete picture of pseudopregnancy (ovary and accessories as in gestation) is obtained by injecting gravimetrically almost equal doses of any one known estrogen (steroid or stilbenoid). The corpora lutea of pregnancy that develop in the ovaries under such treatment contribute the agent that either alone or in conjunction with estrogens (in- or extrinsic) elicits the progestational reactions of the accessories. Here a new technical problem arises. It is current knowledge that so far as the rabbit's uterus is concerned successive synergism between estrogens and progesterone is the preferential mode of treatment. It is even emphasized that a delicate dose balance exists between the two types of agents. Estrogens, though facilitating the progestational reaction, soon interfere with it on simultaneous and careless combination, the estrous reaction overriding the progestational. Both the relayed progestational reaction to estrogens and the combined treatment with estrogens and progesterone simultaneously in rats, cast doubt upon the validity of the thesis that in the contest estrogens soon tend to prevail. Similar lack of interference sufficient doses of progesterone provided, has already been reported in human and primate subjects. Therefore not only the minimal dose of estrogens, needed to pave the way of the progestational reaction in rats, seemed interesting, but also the greatest dose that would not interfere with the 'natural' relayed progestational reaction and with that due to combined estrogen-progesterone treatment. Five or even 10 mg. estradiolbenzoate daily (in 1-2 ml. oil) will still produce the full relayed progestational reaction in 14 days. Likewise combining 3 mg. progesterone with 1 mg. estradiolbenzoate daily results in progestational (and not in estrous) accessories in

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castrate rats. One is therefore justified in concluding that in rats most of the progestational reactions above certain thresholds are not interfered with even by high doses of estrogens. This leads to the next inference, that where advanced pregnancy is disturbed by ultra-physiological doses of estrogens, their most probable toxic point of attack must lie in the fetus and the response is beyond the realm of a hormone action.

ZEUTHEN, ERIK (Copenhagen). Oxygen consumption during cell division.

Modified cartesian divers were used in a reinvestigation of the possible respiratory rhythm during the early cleavage period of eggs.

On single eggs of the frog (*Rana platyrrhina*) the rate of oxygen consumption was found to fluctuate synchronously with the first three cleavages, each cleavage furrow appearing during a period of increased respiration. Small lots of 200 eggs of the sea-urchin, *Psammechinus miliaris*, were studied during the whole cleavage period, embracing 8-10 successive divisions and resulting in the formation of the hatching blastula. According to *Lindahl*, the increase in respiration during this period follows an S-shaped curve. This curve was found to be superposed by waves, always appearing a short time after the cytoplasmic division. Inconclusive indication is in favour of the assumption that the increase in respiration coincides with the resynthesis of the daughter-nuclei.

The respiration is recorded in an air bubble situated close to the eggs. Since, however, no shaking is employed, a diffusion path is intercalated between the air bubble and the metabolic centers, this leading to a certain damping and delay in the recordings. *Linderstrom-Lang*, taking this into consideration, found the experimental results obtained on the frog egg to indicate that the respiratory activity inside the egg varies by some 7-11% of the respiration found in the minima between the waves. The results of the studies of early cleavages in the sea-urchin egg are very similar. In later cleavages, however, the amplitude of the respiratory waves amounts to 20-30% of the respiration in the minima.

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BARKER, S. B. (Iowa City). Effect of thyroid activity upon metabolic response to dinitrophenols.

The early work on the metabolism-stimulating effects of the dinitrophenols stressed the direct action of these drugs on the tissues of the body. However, considerable evidence has been accumulating to suggest that the level of thyroid gland activity alters the metabolic response to the dinitrophenols.

It has been found that 10 mg. of dinitro-ortho-cresol injected intraperitoneally per kg. body weight into normal albino rats produced a 38% increase in oxygen consumption for the first hour. When animals rendered hypothyroid by means of thiouracil were given the same dose, the increase was only 13%. When the drug was administered to hyperthyroid animals, an increase of 83% was obtained.

In contrast to these *in vivo* effects of dinitro-ortho-cresol, the *in vitro* addition of the drug increased the oxygen consumption of various tissues excised from hypothyroid animals to at least as great an extent as it did the oxygen consumption of tissues from hyperthyroid. In many instances, the effects on the hyperthyroid tissues were unquestionably less than the normal or hypothyroid. Diaphragm, kidney, liver, brain, testis, and thyroid were studied.

It has been suggested that the dinitrophenols might stimulate metabolism by effecting a release of thyroid hormone. Although this concept would explain the above results, it is unlikely, considering the marked differences in time relations of the response to a dinitrophenol (a few minutes) and to thyrotrophin, known to stimulate the thyroid gland (many hours). Furthermore, no histological alterations in the thyroid gland have been found in a series of rats given for 14 days, 4 injections per day of 15 mg. dinitrophenol per kg. body weight.

BOYER, P. D. (St. Paul, Minn.). The combination of modified serum gamma globulin with native proteins.

These studies were initiated to determine if one protein might be modified by a procedure which would result in its combination with a second, native protein. In particular, possible combination of serum gamma globulin with other proteins has been studied because

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of the known similarity of the properties of antibodies and serum gamma globulin. The results of the studies have shown that it is possible to bring about combination of modified serum gamma globulin with other proteins which have not been subjected to modifying agents.

The effectiveness of various procedures, such as treatment with guanidine, urea, heat, or alkali for exposing active or combining groups of the globulin molecule on the resulting combination have been studied. The most favorable technique has been to bring about an unfolding of the globulin molecule by exposure to guanidine hydrochloride solutions followed by a careful slow addition of this solution to a rapidly stirred solution of the protein with which the combination is to be effected. When the guanidine concentration is lowered by dilution in the absence of a second protein, the reactive groups of the globulin molecules combine with each other to form precipitates. However, if this dilution is made by introduction into a relatively concentrated solution of another protein, the unfolded globulin may be made to combine with the native, non-modified protein present. The precipitates which form contain a high proportion of the second protein together with the gamma globulin.

Studies have been made on the interaction of the modified globulin with enzymes, other proteins, and with proteins coupled with diazotized sulfanilic acid or aniline. The use of the colored diazo protein derivatives allows accurate evaluation of the composition of the precipitates which form. Results with diazo casein derivatives and with native casein show that with suitable conditions as much as one-half of the precipitates formed may be casein. Results with crystalline urease solutions show that 10 to 20% of the enzyme activity may be removed with the precipitate. Suitable controls have demonstrated that without gamma globulin present in the guanidine solution, no changes in the non-modified proteins result. In addition to the combinations with globulin which resulted in precipitation, a smaller amount of soluble complexes were formed. The effects of modification of the concentration of reactants, time of exposure and addition, temperature, and other conditions have been studied. Optimum conditions for combination have been defined. An interesting observation is that with surprisingly low concentrations of globulin which have been exposed to guanidine for extended

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periods it is possible to obtain temporary gels consisting almost entirely of casein.

Previous work by other investigators has shown that combinations of proteins may be obtained when a mixture of proteins are exposed to denaturing agents. The results presented herein differ in an important aspect, namely that combination may be obtained even though one protein has not been subjected to change, and thus open a new era of investigation.

FISHMAN, WILLIAM H. (Chicago). 'Metabolic Conjugation':
beta-glucuronidase and the physiological action of the
estrogenic hormones.

'Metabolic conjugation' is a term proposed to replace 'Detoxication' in referring to the role of the conjugation mechanisms of the organism. These should be considered normal processes of metabolism. As evidenced by the excretion of steroid glucuronides in human pregnancy urine, glucuronide conjugation may play an important part in the utilization of the sex hormone by the tissue.

The enzyme, beta-glucuronidase, is believed to function *in vivo* in the catalysis of glucuronide conjugation, on the basis of experiments in which several tissues of the body increased their content of enzyme in response to feeding the glucuronidogenic substances, borneol and menthol.¹ Its participation in the formation of estrogen glucuronides seemed probable from other experiments.² A marked decline in uterine glucuronidase was observed in mice after ovariectomy. The beta-glucuronidase level of the uterus in these animals was restored by injection of estrogen.

In the present experiments, the nature of this response to estrogen by tissue glucuronidase was investigated in detail. The effective dose of estrogen was very small, well within physiological limits. The response has been elicited in the case of every one of the estrogens tested. These were estriol, estradiol, estriol glucuronide, and stilbestrol. The injection of non-estrogenic substances which are known to be conjugated with glucuronic acid had no effect on the uterine enzyme. There was no alteration in the beta-glucuronidase activity in liver, kidney, and spleen even though relatively large doses of estrogen were given. Testosterone propionate did not prevent the

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glucuronidase response to estradiol benzoate. The duration of glucuronidase elevation was related to the duration of estrogen stimulation and did not appear to be the consequence of tissue growth *per se*. From these data, the opinion is advanced that beta-glucuronidase plays a role in the physiological action of the estrogenic hormones.

On the basis of this hypothesis, a study was made of the blood glucuronidase of pregnant women. This was expected to show some alterations in view of the fact that substantial amounts of steroid hormone are conjugated with glucuronic acid in human pregnancy. It was found that as pregnancy progressed, beta-glucuronidase activity increased in the red cells and plasma.

Since mammary tumors have been induced in animals by the prolonged administration of estrogens, the beta-glucuronidase activity of various tumor tissues obtained at operation was studied. In carcinoma and cyst of the breast, the tumor contains from ten to twenty times as much glucuronidase as the normal breast tissue. Less striking differences occur in cancer of the esophagus and stomach. This suggests that in humans, significant amounts of estrogen may accumulate in breast tumors and perhaps in tumors of other organs of the body.

¹ Fishman, W. H., *J. Biol. Chem.* 136, 229 (1940). ² Fishman, W. H., and Fishman, L., *J. Biol. Chem.* 152, 487 (1944).

GRANIT, RAGNAR (Stockholm). Nerve fibre differentiation by thermostimulation.

Brief review of work on thermopotentials and thermic excitation, carried out at the Nobel Institute for Neurophysiology by C. von Euler (*Acta Physiol. Scand.*, Suppl. 45, in course of publication), Granit and Lundberg, and Granit. It has been established that moderate warming of a nerve to 45° in a thermode selectively stimulates the small fibres, while cooling stimulates the large fibres. C. v. Euler has discovered that the thermopotentials to heat and cold in vegetative nerves (thermode region negative to normal nerve) appear in fibres of different size. Granit and Lundberg have studied somatic reflexes set up by thermostimulation and found different patterns depending upon the direction of temperature change. Granit

has recorded the thermopotentials in the roots. There is a smaller response to heat and a larger one to cold. Evidence is being produced that these responses arise in different fibres.

GRENELL, R. G. (New Haven, Conn.). The effects of adrenal cortical extract on the electrical activity of the brain.

As a result of observation of the edema and blood vessel damage consequent on arrest of the cerebral circulation (Central Nervous System Resistance. I. The Effects of temporary arrest of the cerebral circulation for periods of two to ten minutes. *J. Neuropath. and Exper. Neur.* 5, 131-54, 1946), it was suggested that adrenal cortical hormone might be a significant factor in protection of the brain from such injury, as well as in the general mechanisms of brain susceptibility. In order to obtain some baseline pattern of adrenal cortical section, two groups of experiments were performed. The first set (similar to those recently reported from the Montreal Neurological Institute) demonstrated that intravenous or intramuscular injections of Wilson's aqueous extract protected the brain from exposure edema. Unanesthetized, curarized, or anesthetized cats and rabbits receiving the hormone showed minimal or no edema grossly and microscopically, and did not evidence the marked flattening of the electroencephalogram shown by the non-injected controls. Trypan blue injected following exposure, appears in the brains of the unprotected animals only. This type of experiment is being continued as a technique for study of the blood-brain barrier.

The second group of experiments were designed to determine the effect of the hormone on the electroencephalogram of the normal, unoperated animal. In the initial experiments, one dose of 2 c.c. per kilogram produced a remarkable increase in amplitude, along with some change in frequency of the brain waves. Intravenous titration of the cortical extract (in 0.25 c.c. per kilogram doses) produced noticeable changes at the level of 0.5 c.c. per kilogram. These increased and finally reached an asymptote at a level between 1.5 and 2.0 c.c. per kilogram. Similar alterations can be observed as a result of topical application of the hormone to local cortical areas only after exposure for several hours. Intracisternal injections in cats have not yet produced these effects. Smaller doses (approximately

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0.18 to 0.2 c.c. per kilo) thus far injected intravenously in man, have brought forth incipient changes of a similar nature in the electroencephalogram.

The observations suggest that adrenal cortical hormones may play a very significant part in the basic physiological mechanisms of brain activity. The results suggest both clinical and physiological applications; the former in protection from or therapy of nervous system edema, post-concussion syndrome, &c.; the latter in studies of the mechanisms of the electroencephalogram and of fundamental neuronal action.

GROSSMAN, M. I. (Chicago, Ill.). **The hormonal transmission of the distention stimulus for gastric secretion.**

The evidence for the existence of a hormone which stimulates gastric secretion is incomplete and inconclusive. That a humoral mechanism for gastric secretion exists has been clearly demonstrated by the fact that in the dog the secretion of an autotransplanted pouch of the stomach is stimulated by the presence of secretagogues in the main stomach. The humoral agent may be a hormone elaborated by the gastric mucosa or it may be secretagogues, present in or produced by the digestion of food, absorbed from the lumen of the stomach. The available evidence suggests but does not prove that secretagogues act by releasing a hormone.

Previous attempts to cause secretion in a gastric transplant by distending the main stomach have been unsuccessful. (Gregory and Ivy, *Quart. J. Exper. Physiol.*, 31, 111, 1941.) In the experiments currently being reported we have repeatedly succeeded in inducing the transplanted gastric pouch to secrete when the main stomach is distended by a balloon.

There are three factors which have operated to prevent the occurrence of secretion in the transplanted pouch when the main stomach is distended. They are: (a) secretagogues constitute a more potent stimulant for gastric secretion than distention; (b) the transplants formerly used have been too refractory (we have utilized $\frac{1}{3}$ to $\frac{1}{4}$ of the fundic portion of the stomach for the transplant); and (c) undue distention of the stomach caused nausea, which is able to inhibit

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secretion by the transplant. (Grossman, Woolley, Dutton, and Ivy, *Gastroenterology*, 4, 347, 1945.)

The demonstration of the humoral transmission of the distention stimulus constitutes crucial evidence for the existence of a hormone for stimulation of secretion of acid by the gastric glands.

HAMMOIR, G. (Liège). **La séparation des myosines α et β .**

La recherche de méthodes de dosage des myosines présente un intérêt particulier, depuis que *Dubuisson*¹ a montré que les extraits de muscles fatigués contiennent des teneurs en myosines α , β , et γ différentes de celles des extraits de muscles normaux. Cet auteur² a déjà mis au point, par fractionnement au sulfate ammonique, une méthode de préparation des deux composantes α et β .

Une étude ultérieure de cette méthode a montré que le sulfate ammonique ne joue qu'un rôle accessoire. On n'obtient un bon fractionnement par ce procédé que si la solution saturée à 27 % a un pH de 5.4-5.5. Or, il est déjà possible d'observer une séparation dans KCl 0.5 m à ces pH. Nous avons déterminé la courbe de précipitation de la composante α d'une myosine d'Edsall dissoute dans KCl 0.5 m en fonction du pH, entre les valeurs de 5.35 et 6.40. α se sépare complètement dans la zone de pH 5.55-5.65 (solution surnageante limpide riche en protéines après centrifugation). Cette propriété n'est toutefois guère utilisable au point de vue préparatif: la zone de précipitation est étroite et la reproductibilité assez peu satisfaisante, certaines myosines pauvres en α ne se séparant pas bien.

Guidé par ces résultats, nous avons mis au point une méthode de séparation basée sur l'insolubilité de la myosine α dans NaAc ou KAc 0.5 m, aux pH inférieurs à 7.5 environ.³

La solution diluée de myosine dans l'acétate molaire à un pH d'environ 7.2, est amenée au pH 7.10 (*Edsall*) ou 7.00 (myosine B). On ajoute lentement, au moyen d'une burette, un même volume d'eau glacée en agitant mécaniquement la solution. La biréfringence disparaît complètement entre 0.6 et 0.5 m. La solution ainsi obtenue de pH 7.50-7.60 (myosine d'*Edsall*) ou 7.15-7.30 (myosine B) donne, après centrifugation, une solution surnageante, limpide, riche en β lorsqu'on part de myosine d'*Edsall*.

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Cette méthode permet de réaliser la séparation aux pH neutres; elle est très reproductible et n'exige qu'une précision relativement grossière des mesures de pH.

¹ Dubuissou, M., *Experientia*, II/7, 258 (1946). ² Dubuissou, M., *Experientia*, II/10, 412 (1946). ³ A paraître prochainement dans *Experientia*.

JACOB, J. (Liège). **Étude électrophorétique des variations de composition d'extraits musculaires de lapin sous l'influence de la fatigue et de la contracture par le monobromacétate de soude.**

Les globulines musculaires solubles entre les forces ioniques de 0.15 et 0.35 sont, essentiellement et à l'état natif, les myosines α et β de Dubuissou.¹ L'une et l'autre deviennent beaucoup moins accessibles à des solutions salines (phosphatiques) d'extraction, lorsque le muscle a été préalablement fatigué jusqu'à épuisement ou contracturé par le monobromacétate de sodium. Toutefois, dans le premier cas (fatigue), c'est la composante α qui est la plus affectée tandis que dans le second (contracture alactacide), c'est la composante β . Ceci semble impliquer une espèce de spécialisation fonctionnelle pour chacune de ces myosines.

¹ Dubuissou, M., *Experientia*, 2, 258 (1946) et 2, 412 (1946).

JUNG, CHARLES (Geneva). **De l'appréciation de la perméabilité rénale par la mesure de l'excrétion uréique.**

Divers auteurs ont cherché à apprécier la capacité fonctionnelle des reins en comparant le taux de l'urée dans le sang et dans l'urine. Des formules connues ont été énoncées en particulier par Ambard et par van Slyke. Elles sont basées sur des observations empiriques, mais laissent à désirer au point de vue théorique.

En se basant sur les lois physiques de la perméabilité et de la diffusion, une tentative peut être faite pour établir une relation mathématique entre les concentrations de l'urée dans le sang et dans l'urine, compte tenu de la capacité de filtration des glomérules. On obtiendrait ainsi une formule générale, dont les énoncés d'Ambard et de van Slyke seraient des cas particuliers ou des expressions approchées.

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On constate toutefois que pour mettre les données du problème en équation certaines hypothèses sont nécessaires et on est guidé dans le choix de ces hypothèses par la nécessité d'aboutir à une formule qu'on puisse aisément rendre explicite. Celle-ci est de la forme:

$$A_0 = A \left(\frac{u}{s} \right)^k$$

où A_0 représente le débit total de l'eau filtrée par les glomérules dans un temps donné, A le débit rénal dans le même temps, u et s les concentrations d'urée dans l'urine et dans le sang.

L'incertitude introduite par les hypothèses préliminaires nécessite une rectification de la valeur de l'exposant k , pour la mettre en accord avec les données expérimentales.

Il est enfin proposé, pour s'épargner les calculs, d'utiliser un abaque qui, les concentrations d'urée dans le sang et dans l'urine et le débit rénal connus, fournit le débit de la filtration glomérulaire, supposé être l'image de la capacité fonctionnelle des reins.

KUBICEK, WILLIAM G. (Minneapolis, Minn.). Renal function in relation to neurogenic hypertension in the dog.

Monopolar shielded electrodes constructed of number 18 fine silver wire supports in a block of molded lucite were placed around both renal arteries and accompanying nerves, around the renal nerves dissected free of the renal arteries, or around the splanchnic nerves above or below the diaphragm. A sinusoidal alternating current of 2-3 C.P.S. and 1-4 volts was then passed through the electrodes. Chronic stimulation of trained, unanesthetized dogs, 20-22 hours per day, for periods as long as 45 days, resulted in an elevated arterial blood pressure. In the absence of renal circulatory pathology blood pressure returned to control levels within 72 hours following cessation of stimulation.

In acute experiments performed on anesthetized dogs renal blood flow was determined with the thermistor-muhr and reduction of blood flow was taken as an indication of renal vasoconstriction. The results of extensive trials with a variety of electrical currents applied to the renal nerves revealed that low frequency (1-5 C.P.S.) sinusoidal alternating currents would produce renal vasoconstriction

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for as long as 2 hours while higher frequencies produced a marked but transient reduction in renal blood flow. No change in renal blood flow was noted during stimulation of the renal arteries alone, while stimulation of the renal arteries and their accompanying nerves, intact renal nerves separated from the renal arteries, the distal ends of the sectioned renal nerves, or the splanchnic nerves, resulted in renal vasoconstriction with no significant change in systemic blood pressure.

In chronic experiments renal plasma flow (RPF) and glomerular filtration (GF) were determined by measuring the rate of excretion of sodium para-aminohippurate and creatinine. In most instances an initial reduction in RPF and GF occurred at the beginning of stimulation. However, after hypertension was established by several days of stimulation (20-22 hours per day) no significant change in either RPF or GF could be demonstrated. It should be noted that renal vasoconstriction must exist if, when arterial blood pressure is elevated, the renal blood flow remains constant, provided that blood viscosity does not change. In conclusion it can be stated that a severe, long-standing hypertension can be produced by appropriate renal artery-nerve, renal nerve, or splanchnic nerve stimulation which persists for the duration of the stimulus and that the observed data do not indicate that renal ischemia is necessary for the persistence of hypertension produced by this technique.

DE LOUREIRO, J. A. (Lisbon, Portugal). **Estimation of the composition of animal food by means of the toluene distillation method.**

The direct estimation of water by means of the *Bidwell-Sterling* method subjects the substrate, during distillation, to an effective extraction of fats and lipoids by hot toluene. If an aliquot of this extract is evaporated it allows an estimation of the fat contents of the substrate. The residue, after the excess toluene is decanted off, after evaporation to dryness contains the dry non-fat-constituents, i.e. in animal foods ash and protein and a small amount of residual fat which may be calculated from the loss on evaporation of the toluene-moistened sample. In a further step the weight of protein may be

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estimated by difference, after ashing the residue. Single minerals may be estimated on the ash.

Advantages of this method are its simplicity and rapidity and the lack of cause of serious error. Actually the whole procedure requires seven weighings and a volume estimation of the distillate water. The crude experimental values and the necessary calculations for the conversion into percentages are conveniently ordered in printed protocols from which an example is given in slide No. 1. Regarding the technique, a modification of the original distillation apparatus is used which allows a perfect drainage of the water distilled and which was described in a previous publication (slide No. 2). The residue of distillation is a porous mass, the ashing of which is particularly easy.

The causes of error have been surveyed and the two main ones are: an error by defect in the estimated value of moisture, due to loss of vapour when the ground-glass joint of the distillation flask is not perfect enough, and an error by excess when the dried residue is allowed to absorb moisture from the air. The other errors are small and the total of the fractions approaches 100% within less than 1% when those two errors are satisfactorily controlled.

OGSTON, A. G., and SMITHIES, O. (Oxford). Some remarks on the oxidative phosphorylation of muscle.

An attempt is made here to examine, as exactly as possible, the data on certain aspects of anaerobic and aerobic phosphorylation.

Thermodynamic information proves to be almost complete in the anaerobic case; the free energy of formation of lactate corresponds well with that required to phosphorylate creatine in the proportions observed.

Information about aerobic phosphorylation is much less complete. The free energy of oxidation of pyruvate under physiological conditions makes a P:O ratio of 3 (creatine as acceptor) just possible, provided that atmospheric O_2 exerts its full oxidizing potential ($E'_2 + 0.82$ volt); but oxidation from $E'_2 + 0.27$ (the E'_2 of cytochrome C) allows P:O to be only 1.8. Critical examination of *Ochoa's* data suggests P:O not greater than 2.5.

If it is true that phosphorylation accompanies only the oxidation

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of substrate by nicotinamide coenzymes, then to develop enough energy for P:O 1.8, the steady-state concentration of free reduced coenzyme must be 10^{-22} molar or less. Unless the reduced coenzyme forms a complex with flavoprotein having a very low dissociation complex, its rate of reoxidation cannot be great enough.

The malate-oxaloacetate system could accelerate the diffusional carriage of hydrogen between proteins, even though it must be both oxidized and reduced by coenzyme I. By working between sufficiently different steady-state ratios of oxidized to reduced coenzyme, it could develop enough energy to phosphorylate creatine. However, this assumption does not ease the kinetic difficulty mentioned above; it raises a further problem of enzymatic specificity, since it would be the unphosphorylated oxaloacetate which would be hydro-generated but the phosphorylated malate which would be dehydro-generated.

It is concluded that a value for the P:O ratio of 3 cannot be accepted in the oxidation of pyruvate and that a value as low as 2 involves difficulties of mechanism. Further work is urgently needed, especially on the following—the value of P:O; the thermodynamics and kinetics of individual stages in the oxidation of pyruvate; the function of the dicarboxylic acids in hydrogen and phosphate transfer; and the possible existence of carrier systems of higher E_0' which could mediate phosphorylation.

¹ Ochoa, *J. Biol. Chem.* 151, 493 (1943).

ÖHNELL, RICHARD F. (Stockholm). Physiological aspects of pre-excitation; a cardiac abnormality.

In pre-excitation, the ventricular part of the heart is repeatedly subjected to an additional excitatory spread, setting in shortly before the start of the regular excitation wave. This additional excitatory spread is connected to auricular activity, starting at a constant interval after the beginning of the P-wave of the electrocardiogram.

In a 'pre-excitation beat' the regular excitatory spread (arriving via the bundle of His) often participates in the excitation of the ventricle. In some instances, however, this is apparently not the case ('pre-excitation without impulse no. 2'). This latter condition may seemingly be due to a delay or non-occurrence of the normal

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impulse, or else to the early spread of the premature wave to central parts of the ventricular conduction system before the regular impulse has had time to pass.

By changes—spontaneous or experimental—of the interval between the starts of the two ventricular excitation waves, different types of s.c. concertina effect (Öhnell, 1942) will be obtained.

During pre-excitation + auricular fibrillation, three different types of ventricular complexes can occur: (1) Normal complexes; (2) wide complexes, due to the abnormal impulse only; (3) all degrees of fusion between these two types.

As regards the mechanism of the abnormal atrio-ventricular connexion, two possibilities will be discussed.

In 1941, the writer reported the case of a family with repeated occurrences of this abnormality. In one member, autopsy revealed two muscular connexions between auricle and ventricle: the bundle of His and in addition a muscle bundle connecting the left atrium with the left ventricle. In this case the QRS time was 0.09 seconds. Wood *et al.* have reported the findings of muscle connexions between right atrium and ventricle.

The other hypothesis to be discussed is the possibility of obtaining ventricular excitation from the mechanical effect of the auricular contraction.

RIKER, WALTER F., Jr. (New York). **Observations upon the neuromuscular behaviour of cats chronically poisoned with di-isopropyl fluorophosphate.**

A syndrome not unlike that of human myasthenia gravis has been produced in cats by the chronic administration of di-isopropyl fluorophosphate (DFP). The course of the poisoning was as follows: Fasciculations which were evident during DFP administration gradually subsided and disappeared entirely by the 3rd to 4th day after the discontinuation of DFP. However, a generalized muscular weakness which varied from complete prostration to ataxic gait persisted for as long as 15 days subsequent to the DFP administration. Following the disappearance of an obvious weakness, and at a time when the animal appeared grossly normal, it was possible to elicit and intensify a syndrome of weakness by means of forced exercise.

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This state of fatigability was evident for as long as 33 days in certain of the animals.

Investigation of nerve-muscle function was carried out on these animals by means of isometrically recorded responses of the gastrocnemius-soleus muscles of the intact cat. Experiments were performed studying: (1) the threshold of response to the close intra-arterial injection of acetylcholine; (2) the ability of the muscle to maintain a tetanus induced by nerve stimulation; (3) the effect of intra-arterially injected acetylcholine on the tetanus. Similar experiments on normal cats provided the control data.

In comparison with normal cats, those chronically poisoned with DFP manifested an increased sensitivity of the muscle to intra-arterially injected acetylcholine; a contractile response was obtained with 0.2 to 0.5 of the amount required in the normal animal. The weakness and fatigability observed clinically in these animals was reflected by the inability of the gastrocnemius-soleus preparation to maintain a tetanus induced by nerve stimulation. When acetylcholine was injected intra-arterially during a failing tetanus, an abrupt transient increase in tension occurred. This is in contrast to the normal in which acetylcholine similarly administered produces a sharp transient decrease in tension. That this defect is primarily synaptic has been demonstrated by the fact that the muscle responds to direct stimulation in a normal manner.

Determinations have been made of the cholinesterase content of the muscle, brain, and peripheral nerve from these poisoned animals. The clinical and physiological recovery of these cats roughly approximated the regeneration of cholinesterase in the brain and nerve.

The fact that DFP produces an irreversible inactivation of choline esterase would suggest that the syndrome of weakness and fatigability may result from an accumulation of acetylcholine at the motor end plate. This seems paradoxical, however, in view of the increased sensitivity of the muscle to acetylcholine and the ability of the acetylcholine temporarily to restore function. The observations do, however, appear to be consistent with a deficiency in available acetylcholine at the neuro-muscular junction. This possibility is as yet unconfirmed since certain *in vitro* experiments fail to indicate a deleterious effect of DFP on acetylcholine synthesis.

It is concluded that DFP exerts an action or actions at the motor

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end plate producing a muscular state similar to that observed in myasthenia gravis, and that this effect is other than that of an anticholinesterase.

THEORELL, HUGO, HOLMAN, RALPH T., and ÅKESON, ÅKE (Stockholm). Crystalline lipoxidase.

Lipoxidase, an enzyme capable of promoting the oxidation of linoleic acid and other polyunsaturated fatty acids by atmospheric oxygen, has been isolated in pure form from soya beans. To follow the enzyme in the course of its isolation the spectrophotometric determination of its activity was used.¹ The method of separation was briefly as follows: Defatted soya meal was extracted with acetate buffer at pH 4.5, and the insoluble matter removed. The extract was brought to pH 6.75 and barium acetate, lead acetate, and acetone were added to precipitate non-active material. The enzyme was precipitated from the mother liquor by ammonium sulfate, redissolved, and additional inactive material precipitated by heating five minutes at 63°. The mother liquor was fractionated with ammonium sulfate, then with alcohol in the cold, and then again with ammonium sulfate. Electrophoresis at pH 6.5 then separated the enzyme from the remaining impurities. Crystallization of the enzyme was achieved by dialysis of a concentrated solution against ammonium sulfate.

The molecular weight and properties of the enzyme will be presented, and the inhibition, substrate specificity, and coupled oxidations will be discussed briefly.

¹ Theorell, Bergström, and Åkeson, *Pharm. Acta Helv.* 21, 318 (1946).

UNGAR, GEORGES (London). Fonction endocrine de la rate.

Deux substances actives ont été isolées de la rate et des recherches ont été poursuivies afin d'établir leur fonction physiologique et leur rôle pathologique. L'une de ces substances (splénine A) peut être produite *in vitro* par action d'une diastase extraite de la rate sur l'acide ascorbique. Sa formule brute est probablement $C_{11}H_{46}O_4$ et elle semble être constituée par une chaîne aliphatique comportant une fonction lactone. La seconde substance (splénine B) peut égale-

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ment être produite *in vitro* par les diastases spléniques à partir du glycogène. Sa constitution chimique n'a pas encore été étudiée.

Il a été établi que la rate déverse la splénine A dans la circulation sous l'influence de l'hypophyse et du cortex surrénal et que cette libération constitue l'un des composants du syndrome d'adaptation de Selye. Elle agit en inhibant l'augmentation de la perméabilité capillaire provoquée par les agressions causales. L'injection de fortes doses de splénine A peut empêcher complètement les lésions hémorragiques produites par l'injection intrapéritonéale de peptone.

La splénine B, dont le mécanisme de libération est inconnu, augmente la perméabilité capillaire provoquée par la peptone. La substance B subit une augmentation considérable dans la rate et dans le sang au cours d'états caractérisés par des lésions hémorragiques, tels que le scorbut et l'intoxication chronique par la saponine. L'injection de fortes doses de cette substance est cependant incapable, à elle seule, de produire des lésions hémorragiques. La splénine B, qui est produite également par la moelle osseuse, est probablement identique à la substance décrite sous le nom de 'throbocytopen' par Troland et Lee en 1938.

Les deux substances exercent des actions opposées. La splénine A diminue le temps de saignement, la fragilité et la perméabilité capillaires et inhibe l'hémolyse provoquée par le système hémolysine-complément, alors que la splénine B augmente tous ces phénomènes et possède aussi une action hémolytique spontanée.

Le mécanisme fondamental de l'action de ces deux substances réside probablement dans une modification de la stabilité du complexe protéase-antiprotéase du sang. La splénine A augmente la stabilité du complexe alors que B facilite sa dissociation.

L'importance physiologique de la sécrétion interne de la rate est probablement faible, mais les perturbations de cette fonction peuvent jouer un rôle considérable en pathologie. Elles peuvent, en particulier, expliquer l'effet de la splénectomie dans certains purpuras et syndromes hémolytiques.

VERZAR, F. (Basel). The action of adrenal cortical hormones (cortin) on cell metabolism.

The problem of how cortin acts on the metabolism of cells has been studied in four different ways since 1939:

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1. It was shown that by minced muscle and liver of adrenalectomised rats and cats phosphorylation of glycogen—the first step of glycogen breakdown—was greatly decreased. Desoxycorticosterone (DOC) and other steroids in a smaller degree brought back the original velocity.¹⁻⁷

2. Minced muscle (normal and adrenalectomised) produces glycogen from glucose-1-phosphate.⁸ It was shown by others and confirmed by us that after adrenalectomy intact muscle (diaphragm of rats) produced glycogen from glucose under the influence of insulin in normal amounts.⁹ In minced muscle a minimum of glycogen has to be present for glycogen synthesis.⁸

3. On intact muscle (diaphragm of rats) DOC and other steroids inhibit glycogen production from glucose with or without insulin.^{9, 10} The inhibition is explained as an increase of glycogen breakdown. This is in agreement with the observations given under 1, that DOC increases glycogen phosphorylation. Thus contrary to the observation on whole animals after adrenalectomy, cortin in isolated muscle and liver does not increase glycogen formation from glucose, but increases glycogen breakdown. We suppose that such an action involves an antagonistic increase of glycogen production from other sources, e.g. proteins.

4. When glycogen is produced from glucose by yeast or by leucocytes, potassium is bound. When glycogen is broken down it is liberated again.^{11, 12} Potassium is transferred from glycogen to myosin, where all three are present in a loose compound in the same place (Q-disk) of the muscle fibre. Stimulation (acetylcholine) first removes the potassium.^{15, 16} A connexion of carbohydrate with potassium metabolism has been shown and also its disturbance after adrenalectomy.^{13, 14}

On the basis of these observations a theory of the role of potassium in muscular contraction was published in 1942¹⁶ and 1943.^{17, 18} and an explanation of adynamia after adrenalectomy was given. The action of cortin is the restoration of this basic cellular metabolic process of glycogen phosphorylation connected with potassium fixation.

¹ Verzár, F., and Montigel, C., *Helv. Chim. Acta*, **25**, 19 (1942). ² Verzár, F., and Montigel, C., *Helv. Chim. Acta*, **25**, 23 (1942). ³ Verzár, F., and Montigel, C., *Verh. Ver. Schweiz. Physiol.* Jan. 1942. ⁴ Verzár, F., and

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WARREN, J. V. (New Haven, Conn.). Hemodynamic observations in patients with large arteriovenous fistulas.

The large number of vascular injuries resulting from the recent war afforded an unusual opportunity to study the effects of arteriovenous fistulas in man. The study of these patients was of interest not only as an investigation of the pathological situation itself, but as a means of investigating the hemodynamics of certain normal circulatory reactions. Observations were made before and after operative eradication of the fistula, and in many patients during temporary occlusion of the fistulas by external pressure.

The cardiac output was determined by means of the critically damped low frequency ballistocardiograph in 47 patients with fistulas intact. In almost half the lesion was of such size that the cardiac output at rest was significantly increased; in some as much as 125% above the normal (postoperative) value. These findings were confirmed in a smaller group of patients in whom the cardiac output was measured by the technique of right heart catheterization utilizing the direct Fick principle. Although in some instances the pulse rate was somewhat elevated, the increased output was primarily due to a large stroke volume. The right atrial, pulmonary arterial, and systemic arterial pressures were found to be within normal limits. The heart size, as determined from the teleoroentgenogram, and blood volume were abnormally large in some instances when compared with normal (postoperative) values. None of the patients studied had evidence of frank cardiac failure.

On sudden temporary occlusion of the fistula by external pressure

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there was a marked diminution in cardiac output in those patients where the resting output was at a high level. Although there was usually a fall in pulse rate, the decreased cardiac output was primarily the result of a diminished stroke volume. Atropinization prevented the slowing of the pulse, but the stroke volume change occurred as before. Ballistocardiographic tracings demonstrated that the decline in stroke volume was extremely prompt, occurring within one or two beats after occlusion of the fistula. Despite this marked change in stroke volume, no change in right atrial pressure was detected. Further evidence that a change in atrial pressure was not responsible for the alteration in stroke volume was obtained from the observation that large changes in atrial pressure produced in these patients by other means failed to produce changes in cardiac output. Although the systemic arterial pressure often rose slightly with the fistula compressed, the pulmonary and right ventricular pressure showed only minimal change.

Following operative eradication of the fistula, measurement of the various cardiovascular functions revealed that all were within normal limits.

These studies demonstrate that in persons with an area of low peripheral resistance, there may be a considerable increase in cardiac output. It appears that this increase in cardiac output is due to a reflex change in activity of the heart itself, rather than as a result of changes in filling pressure. The absence of changes in pulmonary arterial pressure despite considerable changes in cardiac output indicate a rapid, presumably reflex, change in pulmonary vascular resistance.

WINTERSTEIN, H. (Istanbul). *Respiration without chemoreceptors.*

The rhythmic action currents obtained from the phrenic nerve of curarized animals persist after the removal of all chemoreceptors, proving that the automatic respiratory impulses do not depend on the presence of the latter.

The action currents increase if the animal is asphyxiated by, stopping artificial respiration or if acids are infused intravenously.

In animals without chemoreceptors, intravenous infusion of acids

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augments the respiratory movements as a consequence of decrease in blood alkalinity, whereas the CO_2 tension is falling. This proves that—in accordance with the reaction theory—also after elimination of the chemoreceptors the CH and not the CO_2 is the regulator of respiration.

If animals without chemoreceptors are exposed to lack of oxygen the respiratory movements are diminished whereas the CO_2 tension of the blood increases. This is another convincing proof that the respiratory centres whose 'excitability' against CO_2 is supposed to be increased by lack of oxygen, are not regulated by CO_2 .

After the elimination of the chemoreceptors narcotized cats and rabbits do not show any more convulsions on bleeding, and the *Kussmaul-Tenner* convulsions produced in rabbits by ligating the four brain arteries are greatly reduced or may entirely fail in narcotized animals.

WOOD, E. H., and CODE, C. F. (Rochester, Minn.). **The physiologic basis of voluntary (self-protective) maneuvers capable of increasing man's tolerance to positive acceleration.**

Procedures which increase arterial pressure at heart level during exposure to acceleration increase man's g tolerance. Utilization of the thoracic musculature to supplement the force of cardiac contraction and initiation of compensatory cardiovascular pressor reflexes have been successfully used for this purpose.

Positive acceleration induces protective pressor reflexes. These reflexes are sufficiently effective to bring about recovery of vision during exposure to accelerations which initially produce a loss of vision. A significant increase in g tolerance can be produced if the onset of acceleration is slowed sufficiently so that there is time for these reflexes to become effective before accelerations which ordinarily produce symptoms are attained.

Sudden increases of intrapulmonary pressure caused by blowing against a closed glottis produce immediate increases in systemic arterial pressure by addition of the increased intrapulmonary pressure to the pressure generated by the heart. However, if the increased intrapulmonary pressure (40–60 mm. Hg) is maintained for longer

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than 5 seconds, a fall in blood pressure occurs consequent to the impairment of venous return to the thorax. The maximum fall in blood pressure is produced when the intrapulmonary pressure is maintained for about 10 seconds with the thorax in the inspiratory position. If the intrathoracic pressure is then suddenly released, a transitory further decrease in blood pressure occurs followed by a hypertensive period of 5 to 10 seconds' duration.

This induced period of hypertension can be utilized to increase *g* tolerance. The maneuver (M-2) is performed by blowing against a closed manometer system so as to maintain intrapulmonary pressure at 40-60 mm. Hg for 10 seconds immediately before *g* exposure. The average protection afforded 23 subjects was $1.3 \pm 0.1 g$,¹ when 15-second exposures to maximum *g* were used.

The initial increase in blood pressure produced by increased intrapulmonary pressure is widely used by pilots to increase *g* tolerance. The most effective maneuver (M-1) utilizing this mechanism consists of a series of rapidly repeated forced expirations through a partially closed glottis coordinated with muscular straining. The average protection afforded 40 subjects using this maneuver was $2.4 \pm 0.1 g$ units.

¹ Standard error of mean, $n = 23$.

ENNOR, A. H., and STOCKEN, L. A. (Oxford). **The distribution and identification of acid-soluble phosphates in the fatty liver.**

It has been established earlier that there is an increased oxygen uptake and an increased acetoacetic acid production in the fatty livers of guinea-pigs treated with carbon tetrachloride. This result may be taken as evidence of an increased metabolism of fat and possibly also of other substances. The known association of adenosine tri- and di-phosphates with fatty acid oxidation at once suggested that these compounds might be present in increased amounts in the fatty liver. Experiments have been carried out on the distribution and the identification of compounds possessing high-energy phosphate bonds and it has been shown that the fatty liver contains these substances in amounts which are considerably in excess of those present in the normal liver. The barium insoluble fraction of trichloroacetic acid

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extracts of the fatty liver contains approximately twice the normal concentration of a compound which is hydrolysed in seven minutes in normal acid at 100°. This has been identified as adenosine di-phosphate.

Evidence has also accumulated indicating the presence in increased amounts of an acid-molybdate labile phosphorus containing compound in the original trichloroacetic acid extracts and which is not precipitable by barium. Because of the importance of acetyl phosphate in intermediary metabolism it was at first thought that this compound might be an acyl phosphate. Such an hypothesis is of interest because of the fact that phosphorylation is an essential part of the mechanism whereby fatty acids are oxidized. If acyl phosphates are formed as a result of such phosphorylation it would then be expected that in a liver which is oxidizing fat at an abnormally high rate there would be a better opportunity for the detection of any such compound. The presence of acyl phosphates has been tested for by a variety of methods but we have been unable to show that these compounds are present.

Other workers who have detected the presence of acid-molybdate labile phosphorus in rat liver have suggested that this is derived from acetyl phosphate but this suggestion has been based upon the assumption that phosphocreatine is not present and specific tests for either compound have not been applied. By means of the α -naphthol-diacetyl reagent we have shown that phosphocreatine is present and that this compound will account for all the acid-molybdate labile material found in the extracts.

There is thus an increase in adenosine di-phosphate and phosphocreatine concentrations in the fatty liver and this is associated with the increased oxygen consumption and acetoacetic acid production. This finding suggests that the increased oxidation of fat (perhaps partially through the Krebs cycle) leads to an increased formation of high-energy phosphate bonds which are stored partially as adenosine di-phosphate and partially as phosphocreatine.

FLOYD, W. F. (London). **Properties of the body-wall muscles of the earthworm.**

Strips of longitudinal and circular muscle of the body-wall of the earthworm exhibit spontaneous rhythmic contractions when sus-

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pended in a suitable physiological saline solution, with a temperature optimum in the range 10–15° C.; *Floyd* (1946).¹ Strips placed in a watchglass (i.e. not under the influence of the tension exerted by the recording lever—usually 100–300 mg. weight) also exhibit this rhythm. The salines used in the present experiments were equivalent osmotically to approximately 0.14 M NaCl solution, and the preparations tolerate changes of 25% in osmotic pressure without marked disturbance of tone or rhythm. The physiological saline used was: NaCl 7.84 g.p.l., KCl 0.2 g.p.l., CaCl₂ 0.2 g.p.l., NaHCO₃ 0.2 g.p.l. (referred to below as 'normal'). In this medium strips have been maintained in an active condition, i.e. contracting spontaneously, for periods up to 20 hours. The earthworms were either freshly dug or kept in the laboratory in moist filter paper for several days.

Ca⁺⁺-free salines containing up to 0.3 g.p.l. KCl stimulate the preparation, increasing tone; the frequency of the rhythm is also increased (e.g. two or three times) and the amplitude diminished. With a high K⁺/Ca⁺⁺ ratio (e.g. 750 mg.p.l. KCl/11.1 mg.p.l. CaCl₂) results are similar. K⁺-free salines containing up to 0.2 g.p.l. CaCl₂ act in the same direction but results are more variable than with Ca⁺⁺-free solutions. Recovery is rapid (e.g. 1–2 min.) on return to 'normal' saline.

With high K⁺ and Ca⁺⁺ content and a K⁺/Ca⁺⁺ ratio near to unity (e.g. 0.75 g.p.l. KCl/1.11 g.p.l. CaCl₂) the tone and rhythm are usually unaffected. Isotonic KCl produces a large and immediate increase in tone usually with complete abolition of the rhythm. Recovery is slow (e.g. 20 min.) on return to 'normal' saline. Salines with a low K⁺/Ca⁺⁺ ratio and high Ca⁺⁺ content and isotonic CaCl₂ have variable effects.

Anaesthetics such as procaine hydrochloride, urethane, methyl and ethyl alcohol, chloroform and ether, abolish the rhythm reversibly, but they show great variability in the duration of their action. Procaine effects are of long duration, e.g. up to 1 hour with 0.1% and immersion for 3–5 min. The depressant action of procaine (e.g. 0.1%) is antagonized by santonin (10⁻⁴–10⁻⁵). Santonin alone is a powerful stimulant, causing vigorous rhythmic contractions at 10–20 per min., as shown by *Trendelenburg* (1916)² who used circular muscle strips for comparing the actions of anthelmintic drugs.

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The eserized preparation (10^{-8} eserine) is sensitive to A.Ch. (10^{-8} – 10^{-6}), as first pointed out for longitudinal muscle strips only by Wu (1939).³ The resting tone is increased but the height of the spontaneous contractions is unaffected. The preparation is probably unsuitable for A.Ch. assay purposes.

¹ Floyd, W. F., *J. Physiol.* 105, 23p (1946). ² Trendelenburg, P., *Arch. Exp. Path. Pharmac.* 79, 190 (1916). ³ Wu, K. S., *J. Exp. Biol.* 16, 251 (1939).

KREBS, H. A. (Sheffield). Synthesis of glutamic acid in animal tissues.

v. Euler, Adler, Günther and Das,¹ and Dewan² have shown that glutamic acid is synthesized in animal tissues when α -ketoglutarate and ammonium ions are available. Various aspects of this reaction have been studied. Glutamic acid was determined by Gale's method which depends on the use of glutamic decarboxylase of clostridium Welchii. The formation of glutamic acid was very rapid in homogenized, but slow in sliced liver of mammals or pigeons. In kidney cortex on the other hand the rates of reaction in sliced and homogenized material were of the same order. QN_2 glutamic acid reached –30 in homogenized guinea-pig liver and –40 in pigeon liver. As the reductive amination is necessarily coupled with an equivalent oxidative process many oxidative reactions were tested and four were found to couple with the synthesis of glutamic acid, viz.: α -ketoglutarate \longrightarrow succinate; l(–) malate \longrightarrow oxaloacetate; β -hydroxybutyrate \longrightarrow acetoacetate; isocitrate \longrightarrow α -ketoglutarate (see also Krebs and Cohen;³ Adler, v. Euler, Günther and Plass,⁴ and Dewan).²

⁴ Adler, E., Euler, H. v., Günther, G., and Plass, M., *Biochem. J.* 33, 1028 (1939). ² Dewan, J. G., *Biochem. J.* 32, 1378 (1938). ¹ Euler, H. v.; Adler, E., Günther, G., and Das, N. B., *Z. Physiol. Chem.* 254, 61 (1938). ³ Krebs, H. A., and Cohen, P. P., *Biochem. J.* 33, 1895 (1939).

LA BARRE, J., et HANS, M.-J. (Brussels). A propos de l'action antibémolytique du glutathion et du B.A.L. dans les intoxications par la cobratoxine.

En se basant sur les phénomènes d'atténuation par le glutathion de la toxicité du venin de cobra signalés par L. Binet, G. Weller et

Ch. Jaulmes,¹ M.-J. Henri Dustin² a noté que ce dérivé sulfhydrilé possède la propriété de supprimer complètement la diminution de la résistance globulaire observée après administration de doses hémolysantes de cobratoxine. L'un de nous, en collaboration avec O. Vesselovsky³ et avec G. Houssa⁴ a apporté des preuves certaines que cette action protectrice était principalement due au fait que le glutathion inhibe l'action toxique et hémolysante de la lysocithine qui se forme normalement à partir des lécithines tissulaires sous l'influence du venin de cobra. On en arrivait donc à expliquer les causes des phénomènes antihémolytiques observés au cours de l'hyperglutathionémie chez les animaux intoxiqués par la cobratoxine.

Dans la présente étude, nous avons étendu nos recherches en utilisant préalablement à l'administration de venin de cobra un autre dérivé sulfhydrilé aimablement fourni par le Professeur Peters et qui porte le nom de B.A.L. Dans ces essais, des lapins de 2 kg. ont été traités par des doses de 25 à 50 mg. par kg. de B.A.L. et soumis après 15 minutes à l'injection de 1 c.cm. par kg. d'une solution de venin à 1 p. 10.000.

Alors que pour les animaux traités par le venin de cobra l'hémolyse est totale pour toutes les concentrations salines étudiées au cours de l'épreuve de résistance globulaire, le début et la fin de l'hémolyse se produisent aux concentrations salines normales lorsque le lapin a été préalablement traité par une dose appropriée de B.A.L.

En conclusion, le glutathion et le B.A.L. atténuent les effets toxiques de la cobratoxine. De plus, le glutathion inhibe les phénomènes hémolytiques dus à la lysocithine formée aux dépens des lécithines tissulaires sous l'influence du venin de cobra.

¹ C.R. Ac. Soc. 204, 1513 (1937).

² Acta Biol. Belgica 1, 242 (1941).

³ Acta Biol. Belgica 3, 123 (1943).

⁴ C.R. Soc. Biol. 139, 64-5 (1945).

ROSSI-FANELLI, A. (Pavia). Myoglobine d'homme cristallisée.

Les données de la littérature sur la myoglobine cristallisée concernent seulement le pigment isolé des muscles d'animaux d'expérience: cheval (*Theorell, Rossi, Roche*), bœuf (*Rossi, Roche*), porc (*Rossi*). Nous nous sommes proposé d'étudier les propriétés et la composition de la myoglobine humaine. Dans un précédent travail (*Boll. Ital. Biol. Sper.* 22, 2, 1947) j'ai obtenu la myoglobine humaine

pure cristallisée à partir des muscles squelettiques. Les caractères cristallographiques sont notablement différents de ceux de l'hémoglobine de la même espèce. Les cristaux se présentent en aiguilles longues et très fines groupées en gerbes subparallèles ou en agrégats sphéroïdaux fibreux rayonnés. L'allongement de chaque cristal est négatif du fait qu'il a eu lieu parallèlement à α . L'extinction est droite. Les cristaux présentent un pléochroïsme marqué avec α' = marron-rougeâtre parallèlement à l'allongement et γ' = jaunepâle perpendiculairement, avec un index de réfraction > 1.514 . La myoglobine humaine a une teneur en Fe = 0,344% et probablement le même groupement prosthétique de l'hémoglobine de la même espèce et de la myoglobine d'autres espèces. La teneur en N = 16,5% est un peu plus faible que dans l'hémoglobine. Nous sommes en train d'étudier la composition en acides aminés.

Ensuite j'ai étudié le comportement spectroscopique du pigment pur: les bandes α et β de l'oxymyoglobine humaine cristallisée sont un peu décalées vers le rouge par rapport aux bandes de l'oxyhémoglobine, leurs axes tombent respectivement à $\lambda = 5815 \text{ \AA}$ 5426 \AA . Les rapports entre les coefficients d'absorption correspondant aux maxima des deux bandes sont différents pour les deux pigments. La métamyoglobine humaine présente (à pH 6, 7) une bande dans le rouge avec l'axe à $\lambda = 6330 \text{ \AA}$. J'ai suivi au spectroscope la formation des hémochromogènes des deux pigments pendant l'action des alcalis en présence d'un réducteur constatant que l'oxyhémoglobine humaine déjà en solution 0,3 N de NaOH se transforme rapidement en hémochromogène; l'oxymyoglobine au contraire, à la même concentration, présente encore les deux bandes caractéristiques α et β . Pour faire apparaître le spectre de l'hémochromogène, dans ce cas, on doit porter la concentration de NaOH à 3 N environ. J'ai noté quelques différences aussi entre la myoglobine humaine et celle de bœuf. Cette extraordinaire résistance en solutions alcalines est un autre caractère distinctif entre les deux pigments, due probablement à la différente composition et résistance à la dénaturation des deux globines.

SCHWAB, R. S. (Boston, Mass.). **The increasing of frequency response of the ink-writing oscillograph by the use of a magnetic wire sound recorder. Its application to electromyography.**

The limitations of the ink-writing oscillograph, such as the one made by Grass, is its failure to respond in a linear fashion to frequencies having a duration of less than 25 milliseconds. For example, the response of a single muscle fibre contraction which is 8 milliseconds in duration has an amplitude less of approximately 20%. The fibrillary spikes of denervation which are 1-3 milliseconds in duration have an amplitude loss of 90 % and are therefore usually not seen in the electromyographic tracings on the ink-writing oscillograph. Increasing the gain of the amplifiers in order to compensate for this brings the record into the noise levels.

Therefore the following method was devised to overcome this limitation of the ink-writer. The electromyograph after going into the amplifier was recorded on the wire of a sound scribe (Sylvania type) at the usual speed of the wire recorder. The wire recorder was then played back at one-quarter of its normal speed through the amplifiers and on to the ink-writer. The electromyogram was then recorded as if the ink-writer were moving at four times its normal speed, and the 2-3 millisecond waves acted as if they were 8-10 milliseconds in duration with a loss of only 25% of amplitude. They are, therefore, faithfully recorded on the ink-writer by this method.

The reason for this type of recording is that instead of film the record is instantly available and the excessive cost of film and a camera are avoided.

The wire recorder is indifferent to slow frequencies because of its magnetic characteristics and therefore is ideal for the short duration spikes seen in electromyography. The frequencies having durations of less than 100 milliseconds appear with marked reduction in amplitude as compared with those having durations of 200 milliseconds which do not appear at all. Thus the slow potentials and other artifacts are eliminated by this method.

As used in our laboratory we obtained the electromyogram directly on the ink-writer from one set of amplifiers and another set goes into

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the wire, so we have a primary and a secondary tracing for comparison. A good deal of material previously invisible on the ink-writer has been brought out by this method. It is best to have a cathode ray or a loud-speaker available to point out frequencies not seen on the ordinary ink-writer which then can be picked up graphically by the wire.

BLASCHKO, H., BÜLBRING, E., and CHOU, T. C. (Oxford). The correlation between inhibition of cholinesterase and antagonism to curare.

A series of substances chemically related to prostigmine were examined both for their anticholinergic activity and for their anticholinesterase activity. The anticholinergic activity was estimated on the rat's isolated phrenic nerve-diaphragm preparation. The action on true cholinesterase was studied on brain tissue (dog's caudate nucleus) with acetylcholine as substrate; and the action on pseudo-cholinesterase was studied on horse serum with benzoylcholine as substrate. A general parallelism was established between the degree of activity as antagonist to curarine and that as inhibitor of true cholinesterase. No such correlation was found between anticholinergic activity and inhibition of pseudo-cholinesterase. The basic nitrogen radicle of prostigmine and its related compounds appears to be indispensable not only for the anticholinesterase activity but also for the anticholinergic activity.

BÜLBRING, E., BURN, J. H., and DE ELIO, F. J. (Oxford). Factors influencing the secretion of adrenaline from the perfused suprarenal gland.

The left suprarenal gland of the dog has been prepared for perfusion with heparinized blood as an isolated organ, and the output of adrenaline in the venous effluent has been determined.

The output was found to be negligible in periods when the blood flow was satisfactory and the blood well oxygenated.

Adrenaline was discharged from the gland when KCN was injected into the blood going to the gland, and also when the oxygen saturation of the blood was reduced by bubbling nitrogen through it.

The liberation of adrenaline by splanchnic stimulation was studied

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in relation to the presence of adrenaline in the arterial blood. When there was little adrenaline in the arterial blood, splanchnic stimulation caused the discharge of only small amounts of adrenaline from the gland. When the adrenaline content of the arterial blood was increased the discharge due to splanchnic stimulation rose steeply. When, however, the adrenaline content of the arterial blood was increased further beyond a certain optimum, the discharge due to splanchnic stimulation declined and was finally abolished.

CERLETTI, A., and ROTHLIN, E. (Basel). **Untersuchungen über die Thermostromuhr-Methode.**

Die Methode der Diathermie-Thermostromuhr von Rein erfuhr von verschiedener Seite Modifikationen, die vor allem den Ersatz der Hochfrequenzheizung durch die einfachere Gleichstrom-Erwärmung anstrebten (direct current heater (DCH)-Stromuhr).^{1, 2} Rein³ hält aber an den von ihm ausgearbeiteten Grundlagen der Methode fest und betont die Unumgänglichkeit der Hochfrequenzheizung. Unsere Untersuchungen hatten zum Ziel, (a) die Angaben von Rein über die Funktionsweise der Diathermie-Thermostromuhr zu prüfen, und (b) das vereinfachte DCH-Verfahren mit der Originalmethode in Vergleich zu setzen.

(a) Modellversuche an isolierten, mit Blut oder Ringer durchströmten Venen und Arterien verschiedenen-Kalibers bestätigten eindeutig die Angaben von Rein und ergaben im wesentlichen folgende Resultate:

1. Zwischen der als Galvanometeraus Schlag registrierten Temperaturdifferenz der beiden Messlötstellen (G in mm.) und der zeitlichen Durchflussmenge (V in c.cm./Min.) besteht eine hyperbolische Funktion, welche durch die Annäherungsformel $G \cdot V^2 = K$ erfassbar ist. Die Kenntnis des Exponenten x als charakteristische Grösse der einzelnen Messeinheit erweist sich nicht nur für quantitative sondern auch für qualitative Untersuchungen als wesentlich.

2. Die Grösse des Galvanometeraus Schlags G ist linear proportional der angewandten Heizintensität. Eichkurven des gleichen Elementes unterscheiden sich bei verschiedener Heizung also nur in den Ordinaten, d. h. sie verlaufen parallel zu einander.

3. Die Heizleistung kann mit ausreichender Genauigkeit aus der

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dosierbaren Stromstärke I und aus dem Widerstand W des durchströmten Gefäßes bestimmt werden (I^2W), wobei W durch Substitution gemessen wird.

(b) Nach Baldes und Herrick arbeitet die DCH-Stromuhr in gleicher Weise wie die Diathermie-Stromuhr. Unsere Modell- und Tierversuche ergaben, dass die unter (a) erwähnten Gesetzmäßigkeiten im Prinzip zwar zu erkennen sind, wegen Inkonstanz der grundlegenden Funktionsfaktoren für eine praktische Auswertung aber nicht in befriedigender Weise erfasst werden können. In Analogie zur Diathermie-Thermostromuhr arbeitet auch die DCH-Methode über den Weg der Bluterwärmung und nicht durch eine Abkühlungsfunktion des Blutes gegenüber der Messanordnung, wie es Shipley, et al.,⁴ auf Grund von Versuchen am physikalischen Modell annehmen. Die Gründe für das Abweichen von den bei Hochfrequenzheizung geltenden Regeln liegen vor allem in der unterschiedlichen Art der Wärmezufuhr. Während durch die Diathermie eine dosierbare Wärmemenge dem Gefäß und Blut aufgezungen wird, ist bei Gleichstrom-Erwärmung nur die aussen an das Gefäß angelegte Energie regulierbar, nicht aber jener Anteil, der durch die Gefäßwand auf das Blut übergeht. Dieser hängt von mehreren Faktoren ab, die insgesamt nicht zuverlässig kontrolliert werden können.

¹ Schmidt, C. F., and Walker, A. M., *Proc. Soc. Exp. Biol. a. Med.* 33, 346 (1935). ² Baldes, E. J., and Herrick, J. F., *Proc. Soc. Exp. Biol. a. Med.* 37, 432 (1938). ³ Rein, H., *Erg. Physiol.* 45, 514 (1944). ⁴ Shipley, R. E., Gregg, D. E., and Wearn, J. T., *Amer. J. Physiol.* 136, 263 (1942).

CRANE, E. E., and DAVIES, R. E. (Sheffield). **The effect of electric current on acid secretion by isolated gastric mucosa.**

The rate of secretion of hydrochloric acid by frog gastric mucosa mounted in a perspex holder between two chambers¹ was determined manometrically and from the changes in pH of the secretory solution. Some mucosae secreted spontaneously, and in others acid secretion could be induced by histamine. Both these types are called *secretive* mucosae in contrast to *resistant* mucosae which could not be made to secrete hydrochloric acid even with histamine. The existence of a change in the electric potential difference across the mucosa which accompanies the onset of acid secretion^{1, 2} suggested that the rate of secretion might be affected if this potential

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difference were altered by passing an electric current through the mucosa.

Our experimental results show that the Q_{HCl} of secretive mucosae was usually between 1 and 4 $\mu\text{l./mg. dry weight/hr.}$ and was increased during the passage through them of a current of the order of 1 ma./cm². enhancing the natural potential difference (secretory side negative). (22,400 $\mu\text{l. HCl} = 36.5 \text{ mg.}$). The Q_{HCl} increase had values up to $1.2 \pm 0.1 \mu\text{l./mg. dry weight/hr.}$ The Q_{HCl} decreased during the passage of a similar current opposing the natural potential difference. The maximum decrease was $2.8 \pm 0.1 \mu\text{l./mg. dry weight/hr.}$ Resistant mucosae, however, produced no detectable amount of acid (Q_{HCl} less than $10^{-4} \mu\text{l./mg. dry weight/hr.}$) with the same or even greater current densities (up to 5 ma./cm²). No acid or alkali was detected with any other part of the digestive tract: the effect is thus specific to secretive gastric mucosa.

Apart from those which are resistant, mucosae have been found in which (a) spontaneous secretion and (b) histamine induced secretion were increased by an enhancing current. In others secretion could be induced first by a current and subsequently by histamine. The rate of secretion was constant during the passage (usually for $\frac{1}{2}$ or 1 hour) of an enhancing current, and generally decreased, sometimes to its pre-current value, after the current had ceased.

It seems likely that the energy needed to produce the hydrochloric acid represents up to at least 30% of the energy supplied by the current at 1 ma./cm². Our calculations show that the efficiencies in Rehm's experiments on live dogs³ are also of this order. We have found that small currents were usually even more efficient than high ones and in one experiment over 70% efficiency was obtained with a current of 0.4 ma./cm².

¹ Crane, E. E., Davies, R. E., and Longmuir, N. M., *Biochem. J.* 40, Proc. xxxvi (1946). ² Davies, R. E., Longmuir, N. M., and Crane, E. E., *Nature*, 159, 468 (1947). ³ Rehm, W. S., *Am. J. Physiol.* 144, 115 (1945).

FREDERICQ, HENRI (Liège). Blocage des synapses du pneumogastrique cardiaque par la caféine.¹

1. A faible dose (0.5 0/00), la caféine renforce l'action cardio-inhibitrice, inotrope et chronotrope négative, du pneumogastrique

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(*H. Fredericq et Z. M. Bacq*, 1938) et de l'acétylcholine (*Oury*, 1937).

2. A forte dose (5 o/oo), la caféine diminue ou supprime au contraire l'action cardio-inhibitrice de fibres préganglionnaires du pneumogastrique cardiaque de la tortue (*H. Fredericq et Z. M. Bacq*, 1938).

3. A forte concentration (5 o/oo), elle ne réduit que dans une très faible mesure l'action inotrope négative des fibres postganglionnaires du pneumogastrique cardiaque de la tortue, action que l'on peut produire en appliquant directement sur l'oreillette des stimuli électriques rythmés, générateurs d'extra-systoles.

4. En somme, la caféine à 5 o/oo agit sur le pneumogastrique comme le fait la nicotine (*H. Fredericq*, 1934, 1936), qui est, par excellence, un poison 'paralysant' des synapses ganglionnaires autonomes (*Langley*).

Conclusion: A forte dose, la caféine gêne la conduction dans les synapses interposées sur la voie centrifuge du pneumogastrique cardiaque.

¹ Note préliminaire dans: *Journal suisse de Médecine*, 12, 451 (1941).

IVY, A. C., HANSON, MARTIN, and GROSSMAN, M. I. (Chicago).

The minimal effective dose of histamine producing gastric secretion in dogs and humans.

Quantitative determinations were obtained of the gastric secretory response to histamine dihydrochloride in the dog and human. The drug was administered either subcutaneously at 10-minute intervals or continuously intravenously. The size of the dose was increased by a factor of two whenever, as indicated by the volume or acidity of collections, there was no increasing response to the previous dose. Juice was collected from fistulas in vagally denervated total pouches of dogs, or was aspirated continuously with Rehfuß tubes from the stomachs of intact dogs and humans.

The minimal dose of histamine base eliciting a response, in 16 experiments on dogs, ranged from 0.02 to 0.08 micrograms per kilogram per minute ($\mu\text{g./kg./min.}$) with an average of 0.03; in 24 experiments the maximal dose, beyond which no increase in acidity appeared, ranged from 0.2 to 2.7 $\mu\text{g./kg./min.}$; the average of these values was 1.1. There was no significant difference from the above

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averages whether dogs with pouches or intact dogs were used, nor did the method of administration change the response. Considerably less variation in minimal or maximal doses appeared in the same animal than between two different animals.

The minimal dose eliciting a response in seven experiments on humans, injected by continuous intravenous drip, ranged from 0.002 to 0.038 $\mu\text{g./kg./min.}$, average 0.008.

In one human a maximal response was obtained with a dose of about 0.2 $\mu\text{g./kg./min.}$ Side effects in humans were headaches and flushes. Headaches sometimes appeared after an increase in the dose of histamine but no correlation could be shown between the headache and a secretory response.

A graph of the acid response against log dose produced an S-shaped curve typical of many pharmacodynamic relations.

KING, E. J. (London), MACFARLANE, R. G. (Oxford), WOOTTON, I. D. P. (London). **The determination of haemoglobin in human blood.**

The efficiency of clinical haemoglobinometry depends upon the random error of the method, and calibration of the standard used. There has been considerable discussion, and some confusion, regarding the latter problem, but little systematic investigation of the errors of clinical methods for estimating haemoglobin. The present communication describes an attempt to provide further information.

Human blood collected at Oxford was divided into sub-samples. On one of these, estimations of haemoglobin content were made by 16 observers each using a number of different methods and instruments. The results obtained were compared with precise determinations of colour made on a sample sent to the National Physical Laboratory, and with iron and gasometric determinations carried out on other samples at the British Post-graduate Medical School and at Oxford. The whole procedure was repeated with blood from 8 different subjects.

The methods tested included a number that are in general routine use, and two instruments specially made for the experiment. One of these was a hollow-wedge colorimeter, the other a visual photometer using a neutral grey wedge and colour-filter; both had optical

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systems to bring the comparison fields together, and were used to test different pigments in common use for haemoglobin estimation.

The efficiency of each method was judged by the magnitude of the coefficient of variation of the ratios of all observers' readings to the iron determination on the corresponding blood sample. The results are given in the table.

<i>Method or Instrument</i>	<i>Haemoglobin Pigment</i>	<i>Coefficient of Variation (%)</i>
Grey Wedge Photometer	Hb O ₂	4.3
" " "	alkaline haematin	4.5
Hollow Wedge Colorimeter	Hb CO	4.7
Grey Wedge Photometer	Met Hb CN	5.2
Sahli: (Zeiss-Ikon)	acid haematin	5.8
Hollow Wedge Colorimeter	" " "	6.4
" " "	Met Hb CN	7.0
Grey Wedge Photometer	Hb CO	7.2
Hollow Wedge Colorimeter	alkaline haematin	7.8
Dare (Recent Model)	Whole Blood	8.5
Tintometer	Whole Blood	8.5
Haldane	Hb CO	9.0
Talquist	Whole Blood	9.7
Dare (Old Model)	Whole Blood	10.2
Gowers	Hb O ₂	10.6
Sahli (Hellige)	acid haematin	10.9

It will be seen that the experimental were generally better than the routine instruments, with the exception of the well designed Sahli-Zeiss Comparator. The visual photometer is both simple and efficient. Methods employing the dilution principle, whole blood, or which lack an optical system for approximating the fields are, in general, inefficient.

As regards the question of the value of the standards used for clinical haemoglobinometry, it has been found during the course of this work that the British Standards Institution Haldane standard is equivalent approximately to 14.7 gm. haemoglobin as determined by iron estimation.

MACFARLANE, R. G. (Oxford). The fibrinolytic enzyme of human blood.

It has long been known that, under certain conditions, blood may develop the power to dissolve fibrin, such activity having been found in the blood of animals following hepatectomy and peptone shock,¹ and in plasma following treatment with chloroform *in vitro*.² Recently it has been shown³ that the supposed fibrinolytic activity of certain strains of β -haemolytic streptococci is really due to their production of an activator (streptokinase) that converts an inert precursor substance (plasminogen) existing in all normal human blood into active proteolytic enzyme (plasmin). This enzyme is probably identical with that activated by chloroform.

Plasma contains plasmin as well as plasminogen, both being associated with the globulin fraction, but the enzyme is normally over-neutralised by an inhibitor, antiplasmin, which is associated with the albumin fraction. Proteolytic activity results from various disturbances of the equilibrium between plasmin and antiplasmin. Chloroform, for instance, destroys antiplasmin; fractionation of the plasma removes it; simple dilution favours the dissociation of its combination with plasmin; and streptokinase activates plasminogen.⁴

The origin of plasmin is unknown, but lung tissue and urine have a high content of a fibrinolytic enzyme resembling plasmin. Spleen extract, on the other hand, is strongly inhibitory.

Spontaneous activity occurs in the blood of human subjects following a variety of disturbing stimuli, such as surgical operation, shock, trauma, anxiety, violent exercise, and in some pathological states.⁵ It can also be produced by the injection of adrenalin, and this observation, coupled with the nature of the other stimuli mentioned, suggests that activation of the proteolytic system of the blood is part of the 'alarm reaction'.

The mechanism by which this activation occurs is at present obscure. It can be obtained in cases of Addison's disease and after splenectomy. Adrenalin has no activating effect on plasma *in vitro*, nor have the leucocytes which increase in numbers in the blood following the administration of adrenalin *in vivo*.

It would seem that the occurrence of this proteolytic activity under the conditions mentioned may be related to some of the phenomena

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of shock, and to the increased protein destruction observed in post-traumatic and anxiety states.

- ¹ Nolf, P., *Arch. Int. Physiol.* 3, 1 (1905). Nolf, P., *ibid.* 6, 306 (1908).
² Nolf, P., *ibid.* 16, 374; 18, 549 (1921). Nolf, P., *ibid.* 19, 227 (1922).
³ Christensen, L. R., *J. Gen. Physiol.* 28, 363 (1945). Christensen, L. R., and MacLeod, C. M., *ibid.* P. 559 (1945).
⁴ Macfarlane, R. G., and Pilling, J., *Lancet*, 2, 562 (1946).
⁵ Macfarlane, R. G., *ibid.* 1, 10 (1937). Macfarlane, R. G., and Biggs, R., *ibid.* 2, 862 (1946). Biggs, R., Macfarlane, R. G., and Pilling J., *ibid.* 1, 402 (1947).

MOE, G. K. (Ann Arbor, U.S.A.) Evaluation of vasomotor reflexes in animals and man by means of Tetraethylammonium ion.

The blockade of autonomic ganglia produced by tetraethylammonium (TEA) permits evaluation of the degree of vasomotor tone under various physiological conditions. In dogs under barbiturate anesthesia, increasing doses of TEA cause progressively greater depressor responses until a 'floor' is reached; greater doses will not lower the pressure further.

A. ANIMAL STUDIES

Vasomotor tone in hypertension and hypotension. Hypertension resulting from carotid occlusion increased the response to TEA, but the 'floor' was not altered. During 'humoral' hypertension resulting from epinephrine infusion, and during plethora, the response to TEA was diminished, indicating reflex reduction of vasomotor tone. During nitroglycerine infusion or after hemorrhage, TEA, by blocking compensatory reflexes, caused a severe hypotension, to a floor lower than normal.

Blockade of pressor and depressor reflexes. During infusion of TEA, carotid occlusion or centripetal vagal stimulation failed to evoke a pressor response; stimulation of Hering's nerve failed to cause a depressor response. Dorsal root dilators, if involved in this reflex, are evidently blocked by TEA.

The pressor response to epinephrine in the intact dog is accompanied by increased femoral arterial flow, and decreased renal flow. During TEA infusion epinephrine decreased blood flow in both areas. Buffer reflexes apparently involve chiefly somatic rather

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than visceral vascular beds; vasodilatation in muscle in response to epinephrine is interpreted as the result of depressor reflexes.

B. HUMAN STUDIES

In man TEA is useful in assaying the role of neurogenic vasoconstriction in various vascular disorders. The drug causes an increased blood flow to the extremities as measured by changes of skin temperature or by plethysmography. Failure to obtain maximal peripheral dilatation suggests organic vascular damage. TEA prevents the peripheral constriction induced in 'hyper-reactors' by exposure to cold.

In supine normotensive subjects the depressor response to TEA is minimal; in most hypertensive subjects the extent of the pressure fall is roughly proportional to the degree of diastolic hypertension. Whether or not hypertension is due to neurogenic causes it would appear that elevated constrictor tone may be a contributing factor.

Postural hypotension, as evidence of failure of vasoconstrictor reflexes, develops in both normal and hypertensive patients. It is present in some hypertensive patients who experience no drop in blood pressure in the supine position. This suggests that in these patients neurogenic vasoconstriction is not an important factor in the hypertension observed at bed rest.

NIMMO SMITH, R. H., and WOODS, D. D. (Oxford). *p*-amino-benzoic acid and folic acid in bacterial growth.

p-aminobenzoic acid (*p*-AB) is an essential requirement for the growth of many bacteria. It is probably required for the growth of most bacteria and is synthesized by those not needing an external source. Furthermore, the growth inhibitory action of sulphonamide drugs is annulled by this substance in a competitive manner. It was therefore suggested¹ that sulphonamides inhibit competitively the enzyme concerned in the utilization of *p*-AB.

'Folic Acid' is another essential metabolite for bacteria. It has recently been synthesized² (pteroylglutamic acid) and the molecule shown to contain a *p*-AB residue. It was therefore considered possible that the latter substance might be required solely for the synthesis of the more complex factor, folic acid. If this were the case it would be expected that organisms requiring *p*-AB acid would

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grow equally well if given folic acid. The synthetic product (pteroylglutamic acid) was tested with a variety of such organisms and was found to promote growth in all cases though the molar concentration required was greater (c. 10-100-fold) than that of *p*-AB.

Pteroylglutamic acid also acted as an antisolphonamide agent with these organisms. With some the nature of this activity differed from that of *p*-AB, in that it was non-competitive. The concentration sufficing to promote growth did so irrespective of the sulphonamide concentration. This would be expected if the main point at which sulphonamides act in these organisms is on the synthesis of this substance from *p*-AB, since the product of the inhibited reaction has been added.

Under conditions in which multiplication does not occur, and in the presence of *p*-AB, *Streptobacterium plantarum* (a *p*-AB requiring organism) synthesizes folic acid, as estimated by growth response of *L. casei* and *Strept. faecalis* R. The synthesis is inhibited by sulphonamides. This technique is being used for more detailed studies of the conversion of *p*-AB to folic acid and the effect of sulphonamides thereon.

¹ Woods, *Brit. J. Exp. Path.*, 21, 74 (1940). ² Angier, *et al.*, *Science*, 103, 667 (1946).

ØRSKOV, S. L. (Aarhus, Denmark). Experiments on active and passive permeability of *bacillus coli communis*.

Very little is known of the permeability of bacteria with the exception of Hoffmann and Ruhland's experiments (1925) on *Beggiatoa mirabilis* (which cannot be plasmolysed).

Fisher (1891) investigated the permeability of different bacteria by following the disappearance of plasmolysis in hypertonic solutions. Some substances permeated so fast that deplasmolysis could not be followed.

My experiments on the permeability of *bacill. coli communis* here agree with Fisher's, but as to the permeating of salts and carbohydrates his results are of little value, which is not astonishing when the time of his experiments is taken into consideration.

Three methods have been used in my experiments:

1. Ordinary cover-slip-slide preparations from the suspensions of the bacilli.

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2. An apparatus for continued examination of suspensions.¹

3. A photoelectric method which has been used by the author to examine the permeability of red blood cells and yeast cells.²

In most experiments the 24-hour-old peptone bouillon cultures are centrifuged and the bacilli suspended in 0.9% NaCl. Deplasmolysis can be followed quantitatively by the photoelectric method. Some substances as glycerol, hexamethylene tetramine and antipyrine cause no plasmolysis.

With urea plasmolysis has disappeared after 1–2 minutes, with malonamide after 6–8 minutes, and these rates are very constant.

In some experiments with glucose, mannite, saccharose and other sugars deplasmolysis goes on at the same rate as found for malonamide, in others much more slowly, and it is found that if the bacilli are thoroughly washed with 0.9% NaCl, deplasmolysis is very slow.

The addition of potassium phosphate (pH 6.5) produces a rapid deplasmolysis. The explanation seems to be that deplasmolysis is caused by an active absorption of potassium phosphate (acetate can also be used) and probably other substances of the broth.

Plasmolysis caused by adding hypertonic NaCl (which permeates very slowly) will disappear after adding KH_2PO_4 , especially when glucose is present.

It seems probable that other kinds of cells will restore their plasma volume in similar ways.

The deplasmolysis can be prevented by 0.1–0.2% potassium cyanide, sodium azide and moniodoacetic acid.

If bacilli coli are thoroughly washed with 0.9% NaCl plasmolysis will also be found in most of the cells, probably because the bacilli lose potassium and other osmotic substances and cannot absorb NaCl.

Analysis of centrifuged bacilli should be able to elucidate the problems.

¹ Demonstrated at this Congress by the author. ² Ørskov, *Biochem. Zeitschr.* **279**, 250 (1935), and *Acta Patholog. et Microbiol. Scandinavica* **6**, 523 (1945).

ROTHLIN, E. (Basel). The fate of ergot alkaloids in the organism.
1. *Elimination.* When rats are given intravenously 5 to 25 mg./kg. of either the natural or the dihydrogenated ergot alkaloids, only

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about 1/1000 of the administered alkaloid can be found in unaltered form in the urine within 24 hours. These alkaloids, when added to urine, are completely recovered and are very stable in urine.

2. *Behaviour in Blood.* Five minutes after intravenous administration, in rabbits, of even maximally-tolerated doses of these alkaloids, only about 0.5% of the injected amount is still present in the blood and, after two hours, the remnants have practically disappeared. Neither the natural nor dihydrogenated alkaloids are bound by the blood and, practically, neither is destroyed.

3. In tissue suspension from liver, kidneys, spleen, or muscles, relatively large amounts of the intravenously injected alkaloids can be recovered. Alkaloids added to such tissue suspensions can be found in amounts up to 60% at the most. The rest is apparently very tightly bound and not rapidly destroyed because these mixtures of tissue suspension plus alkaloid show the same adrenolytic activity for many hours when kept at room temperature and at 37°.

4. In no brain-section was it possible to recover any amount of alkaloid after intravenous injection. Also, recovery from cerebrospinal fluid and aqueous humour is uncertain because these body-fluids themselves often exhibit a weak adrenolytic activity.

The difference between the definitely positive recovery from the liver, spleen, &c., and the absence of recovery from the brain is due to the blood-brain barrier. This is also proven by the fact that *intraventricularly* administered alkaloid is much more toxic than the same amount of alkaloid injected intravenously.

Since, after intravenous administration, central effects occur, it is assumed that the threshold for certain brain centres is so low that the method employed in all these submitted experiments, i.e. the adrenolytic activity upon the isolated seminal vesicle of the guinea pig, is not sensitive enough for recovery of the alkaloids in the brain. This is in spite of the fact that this biological method permits recovery of the unaltered alkaloids in amounts as low as 0.05 to 0.0017 g./ml., corresponding to the different adrenolytic activity of the natural and dihydrogenated alkaloids of ergot.¹

¹ Rothlin and Brügger, *Helv. Physiol. et Pharmacol. Acta*, 3, 519 (1945).

WERTHEIMER, E., and TUEKISCHER, E. (Jerusalem). **The in vitro synthesis of glycogen in the diaphragm of normal and alloxan-diabetic rats.**

The synthesis of glycogen in rat liver slices depends on the presence of potassium in the medium (*Hastings and Buchanan*). Synthesis in the rat diaphragm, on the other hand, is inhibited by potassium. A potassium-free phosphate buffered saline solution proved to be the optimal medium for synthesis of glycogen in the rat diaphragm. Addition of potassium, even in physiological concentrations, decreases the synthesis of glycogen. At higher concentrations of potassium, glycogenolysis takes place instead of synthesis.

The enhancement of glycogen synthesis in the diaphragm by insulin (*Gemmill*) can be demonstrated in potassium-free as well as in potassium containing medium. With serum as medium, however, insulin has no enhancing effect.

The synthesis of glycogen in the diaphragm of alloxan-diabetic rats incubated with serum of alloxan-diabetic rats was markedly lower than the synthesis by the diaphragm of normal rats incubated with serum of normal rats at correspondingly high glucose concentrations. Incubation of the 'diabetic diaphragm' in 'normal serum' increased the synthesis, whereas incubation of the 'normal diaphragm' in 'diabetic serum' decreased the synthesis. Addition of insulin to the 'diabetic serum' or addition of a 'normal serum' concentrate to the 'diabetic serum' or incubation in serum of insulin-treated alloxan-diabetic rats increased the synthesis in the 'diabetic diaphragm'. Addition of insulin to normal pooled serum (glucose concentration 100 mg. %) distinctly enhanced the synthesis of glycogen in the 'diabetic diaphragm', whereas no such effect could be observed under these conditions in the 'normal diaphragm'.

No differences, however, between the synthesis of glycogen in the diaphragms of alloxan-diabetic and normal rats were observed in the different salt media. In these media the effect of insulin on the 'diabetic diaphragm' was even smaller than that observed in the 'normal diaphragm.' These results make it further clear that demonstration of metabolic changes of tissues in vitro may become manifest only in a correspondingly changed serum milieu and may be undetectable in an indifferent salt medium.

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Adrenaline completely inhibits the glycogen synthesis in the rat diaphragm under optimal conditions of synthesis and as known favors glycogenolysis (*Cori*). Ergotamine paralyses the effect of adrenaline, while no clear-cut effect of insulin can be observed.

Glycogenolysis in the rat diaphragm was favored by potassium. Insulin had no influence on the rate of glycogenolysis. The order of magnitude of this process was the same in the 'normal' and in the 'diabetic' diaphragm.

ABDON, N.-O. (Lund, Sweden). **On the mechanism of choline deficiency.**

In a series of communications we have shown the presence of a new choline compound, the acetylcholine precursor.^{1, 2} Experiments showed, however, that this substance is not only the immediate source of the cholinergic transmitter, it is also connected with purely muscular functions.³⁻⁶ To get further knowledge about the role of the precursor we studied rats fed on a practically choline free diet. We found that before the usual signs of choline deficiency appear there is a decrease in the ability of the muscles to decolorize methylene blue in vacuo or to consume oxygen in Warburg respirometers. Addition of choline, acetylcholine, lecithine, or methionine had no effect in vitro, while injection of choline into the animal only 60 min. before it was killed for experiment normalized the metabolism of its muscles. Thus, the choline must pass the body to be active. It is thereby changed into a dialyzable biocatalyst. This can be extracted from muscles as well as other organs from animals on a normal diet according to the same methods as we have previously used in preparing the acetylcholine precursor.⁷⁻⁹ Recent experiments, which will be reported at the meeting, seem to show that the new co-enzyme is identical with the acetylcholine precursor.

^{1, 2} *Acta Physiol. Scand.* 8, 75 (1944); 8, 103 (1944). ³⁻⁶ *Acta Pharmacol.* 1, 1; 1, 162; 1, 169; 1, 325 (1945). ^{7, 8} *Nature*, 158, 793 (1946); 159, 272 (1947). ⁹ *Acta Pharmacol.* 3, 73 (1947).

BATE-SMITH, E. C., and BENDALL, J. R. (Cambridge). **Rigor mortis and muscular fatigue.**

The authors have recently shown¹ that the stiffening of mammalian muscle in rigor, which occurs whether or not acid is produced in

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the muscle, is invariably accompanied by a decrease in the combined adenosine di- and triphosphate content of the muscle.

Severe muscular exercise immediately before death results in a considerable decrease in the amount of lactic acid produced in the muscles after death. When little lactic acid is formed the onset of rigor is hastened.

Except in a condition of fatigue or undernourishment, muscle normally contains enough glycogen to enable pH 6 or less to be reached in rigor, and if this is the case the onset of rigor is delayed until the muscle reaches pH 6.2, approximately, whereupon rigor sets in and is completed, as a rule, in 2 hours. The length of the period of delay before commencement of rigor depends to a marked degree upon the muscular activity of the animal immediately before death, and the length of this period can be deliberately shortened or lengthened by administration of substances which, on the one hand cause convulsions, or, on the other hand produce muscular relaxation.

Records will be shown of instances in which (a) instantaneous onset of rigor in rabbits' muscles has been induced by injection of insulin, and (b) the period of delay has been increased to as long as nine hours by injection of myanesin. Apparatus designed to provide a continuous record of the development of rigor in the psoas muscle of the rabbit will be demonstrated.

For the glycogen content to be materially decreased, exercise must take place under hypoxic or hypoglycaemic conditions. In the initial stages of exercise, until an efficient circulation of the blood is established, conditions are hypoxic, and appreciable loss of glycogen from the muscles then occurs. In struggling on the slaughtering floor, for instance, an animal may show an increase of 0.2% of lactic acid in the blood, representing a loss of approximately 0.1% of glycogen from the muscles. Such a loss may be serious, since the proper keeping of meat depends upon the lowering of pH in rigor to the normal value of well below 6.0.

If rats are exercised at a rate higher than that of the steady state, collapse ensues due to continued tissue hypoxia. The condition of the collapsed animals corresponds with that seen in shock due to a wide variety of causes² and in particular appears to be identical with traumatic (drumming) shock attributed by *Noble* and *Collip*³ to tumbling in the drum. In the present authors' experiments shock,

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in many instances fatal, appears to be due to exercise alone. Resistance to collapse, corresponding to the resistance to drumming shock described by Noble⁴ and Noble and Toby,⁵ is established extremely readily. A single period of severe exercise leading to collapse prevents collapse during subsequent bouts of exercise of the same severity and much longer duration. This protective effect is thought to be due to the rapid establishment of an efficient circulation of blood during the early stages of exercise in the resistant, i.e. 'trained', animal.

¹ *J. Physiol.*, in the press. ² *Ann. Rev. Physiol.* 8, 335 (1946). ³ *Q. J. Exp. Physiol.* 31, 187, 201 (1942). ⁴ *Amer. J. Physiol.* 138, 346 (1943).
⁵ *Canad. J. Res.* 22 E, 79 (1944).

BELL, G. H. (Glasgow). **Chemical and physical properties of bone in rickets.**

The strength and the chemical and crystalline characteristics of the bones of rats and dogs fed on a rachitogenic diet have been investigated. The strength of the rachitic bones is reduced in proportion to the reduction in the ratio of inorganic to organic material in the bones. The structure of the apatite and collagen as revealed by X-ray crystallography is not different in the normal and rachitic specimens. Although the bones are weak in rickets this is insufficient in itself to explain the deformities which occur. These must be presumed to be due to an abnormal working of the modelling process in the absence of vitamin D.

BENA, E., and FIŠER, O. (Prague). **The analysis of the dynamics of brain action.**

Successive induction and other recovery processes following excitation may be compared with physical models and studied from the point of view of physical formulae.

I

The return of the pulse rate after 5 times knees-bend or after the release of pressure on the eyeballs, both cases of successive induction, are comparable to a damped oscillatory motion, two forms of which occur, as follows:

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1. In the first form the damping of the oscillatory motion is smaller than the angular velocity. The equation expressing this form of oscillatory motion (in this case the form of the return of the pulse rate to normal in the oculocardiac reflex) at any time, t , may be expressed as follows:

$$\phi(t) = 2,48e^{-0,04t} \cdot \cos \frac{2\pi t^{1,55}}{419}.$$

2. In the second form damping of the oscillatory motion becomes greater than the angular velocity. This form of oscillatory motion, the so-called aperiodic motion, may be described by:

$$\phi(t) = 15,622 e^{-0,0458t} - 9,195 e^{-0,0809t}$$

Conclusion

The return of the pulse rate to basal values is a case of successive induction, which can be proved to be a simple damped oscillatory motion, either over- or under-damped. In this motion 2 forces are acting: one elicited by the excitation of the oscillatory system of vago-sympathetic and the other by the resistance acting against this oscillation.

II

The exercise of 5 times knees-bend was combined with the eliciting of the oculocardiac reflex. 5 secs. following the completion of the knees-bend the bulb pressure was started and continued for 5 secs. The pulse rates observed were calculated and adjusted by the sum of 5 exponential functions:

$$\phi(t) = 7,6270 e^{-0,00280t} + 23,6316 e^{-0,10432t} \cdot \cos(11065 \cdot t + 78^\circ 29') - 1,9265 e^{-0,5410t} \cdot \sin(45995 t + 5^\circ 21' 36'')$$

Conclusion

The form of the return of the pulse rate in this combination of two stimulations is conditioned by 3 reflexes which can never be isolated by experimental methods:

- (a) The first slowly reduces the pulse rate to basal values;
- (b) the second is probably an expression of two excitations of the vagus, one from the successive induction, and the other from the oculocardiac reflex;
- (c) the third is like a damped oscillation but of unknown origin (it may perhaps be due to respiration).

III

The return of the pulse frequency to basal values after the Valsalva effort may be adjusted by the sum of 3 exponential functions:

$$\phi(t) = 11,212 e^{0,000767t} + 6,571 e^{-0,0792t} \cos(0,117t + 6^\circ 30' 27'')$$

Conclusion:

The form of the return of the pulse rate after the Valsalva effort is conditioned by 2 reflexes:

1. The first is a damped oscillation.
2. The second slowly increases the pulse rate (this may be due to the needs of the coronary circulation).

BRODAL, A. (Oslo). Experimental investigations of fibre connections of the olfactory system.

The investigations to be reported are part of a programme of research on the connections of the olfactory system which is being carried out in the Department of Human Anatomy, Oxford.

The origin of some of the fibre tracts has been studied in rats and rabbits by investigating the retrograde changes in the nerve cells following interruption of their axons. These changes are not characteristic in adult animals and, therefore, the modified Gudden method developed by the author has been utilized, for it gives more clear-cut results. The origin of the fibres of the anterior commissure will be considered more particularly in this communication.

BROWN, G. L., and BURNS, B. DELISLE (London). Effects of fatigue on mammalian muscle.

The effects of repeated stimulation of the III nerve on neuromuscular transmission in the inferior oblique muscle of the eye have been studied in decerebrate cats. This muscle shows two electric responses (B_1 , B_2) to the second of a pair of maximal motor nerve volleys at intervals of 1-2 msec. The first of the two responses (B_1) does not appear to be an end-plate potential, but to arise from fibres needing two incident volleys to excite them. The second (B_2) is the usual response from the partially refractory system. A brief tetanus may cause the disappearance of the B_1 response. These two responses are used to analyse the effects of fatigue on the neuromuscular system.

CONWAY, E. J., and BRADY, T. (Dublin). **The source of the hydrogen ions in the large K and H exchanges across the yeast cell membrane during fermentation.**

It has been shown that pH values as low as 1.7 could be obtained when baker's yeast ferments glucose and KCl are introduced into the unbuffered suspending fluid. Brewer's yeast behaves in a similar way. When the baker's yeast is subjected to some days oxygenation prior to the fermentation, the pH value could generally be obtained as low as 1.6, and a value of 1.4 has been obtained.

The search for the source of the H ions has shown that succinic acid and acid-labile CO_2 (Ba-insoluble) provides almost all the H ions. The lower the pH is driven by prior oxygenation the more the carbonic acid system provides the H ions, and the succinic source markedly decreases.

The exchange of the K and H ions occurs in an outer metabolic chamber of the yeast cell. This chamber is bounded internally by a membrane impermeable to succinic, malic, pyruvic acids, also to a number of amino acids studied, but is freely permeable to acetic, propionic and butyric acids. Acetic acid penetrates the whole cell freely and is concentrated inside as the acetic anion. Succinic and pyruvic acids, both of which are formed within the cell, have a concentration ratio relative to the external solution of only about 0.2.

DIAS, M. V. (Rio de Janeiro). **The excitatory action of thiamin on the central nervous system.**

It is generally stated that Vitamin B₁ (thiamin) exerts an influence on the nervous functions, but until now it was not exactly known if this influence is only indirectly dependent from its rôle in the oxidative processes of carbohydrates, or whether thiamin can intervene also in a more direct manner on the nervous processes, in a close association with acetylcholine, as was recently postulated.

We therefore performed a series of experiments on 60 dogs, applying the referred substance directly and circumscribedly to the cerebral 'motor' cortex. The 'motor' points which elicited by electrical stimulation contractions of the contralateral eyelids (*m. orbicularis oculi*), and extension or flexion of the contralateral forelimb, were determined by unipolar excitation.

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Thiamin hydrochloride was used in solutions of 1-2-5 and 10%. A small square filter paper 2.5 to 3.5 mm. square, was soaked with the solution assayed and was directly applied to one of the 'motor' points previously located. All observations were made on animals in an unanaesthetized state.

It was observed that thiamin hydrochloride (1 to 10% sol.) applied directly to the cerebral cortex, after 1 to 2 minutes, gives rise to rhythmic contractions (clonus) of the muscle or muscular group corresponding to the cortical 'motor' point submitted to the action of the drug. Initially, the motor reactions are weak, but generally, within one to three minutes after their appearance, when 2% to 10% sol. were used, the clonus becomes stronger and better characterized.

Usually, apparent repetitive mechanical stimulation on the cutaneous region that covers the muscle in rhythmic action increases the intensity and the frequency of the motor reactions.

In several animals, with peripheral cutaneous stimulation or simply spontaneously, it was possible to observe the occurrence of progressive generalization of the motor reactions to other muscular groups, in a jacksonian manner, and the appearance of typical epileptiform convulsions, which evolve with the typical tonic-clonic sequence.

In 3 dogs, a weak clonus was obtained by one application of 0.5% thiamin hydrochloride sol., soaked in a filter paper of 2.5×3 mm. on a cortical 'motor' point. Such a filter paper absorbs 0.0020 to 0.0025 cm.³ of the sol., that corresponds to 10 to 12 γ of thiamin hydrochloride.

In another way, it was verified that injection of thiamin hydrochloride in the cerebral lateral ventricle of dogs and cats, induces the appearance of localized or generalized motor convulsive reactions.

Some experiments were made with diphosphothiamin (co-carboxylase) in 2 and 5% solutions, applied directly and circumscribedly to a cortical 'motor' point. Identical results were observed to those obtained with thiamin hydrochloride. All animals presented localized muscular clonus, and in 2 of the 5 dogs studied, generalized epileptiform convulsions were observed.

Experiments were made with the two separate thiamin moieties:

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pyrimidine and thiazole. The cortical application of 2-methyl-5-ethoxymethyl-6-aminopyrimidine (10% sol.) and 4-methyl-5-*beta*-hydroxyethylthiazole (pure liquid substance) gave negative results, no motor reactions being observed. Each of the two substances was applied to the cerebral cortex during 30 minutes, the drug being renewed every 6 minutes.

Other hydrosoluble vitamins: pyridoxine hydrochloride (5% sol.); niacinamid (5 and 10% sol.) and ascorbic acid (5 and 10% sol.) applied to the cerebral cortex for 30 minutes, with regular renewal of the substances, proved to be ineffective in producing any kind of muscular reaction.

FOLLEY, S. J., and MALPRESS, F. H. (Belfast). Some observations on oestrogen-anterior pituitary relationships.

It has become necessary, particularly in the light of recent work on the artificial induction of lactation in dairy animals by synthetic oestrogens,¹ to reassess earlier theories claiming that oestrogens are purely inhibitory in their action upon the lactogenic function of the anterior pituitary. Developing a tentative explanation put forward by Folley and his co-workers² the authors suggest that the experimental results of the use of oestrogens for inducing lactation can best be interpreted by postulating a range of stimulatory oestrogen concentrations within which secretion of the lactogenic hormone complex of the pituitary is increased; below this range no effect either stimulatory or inhibitory can be observed, while above it oestrogens exert their more familiar inhibitory action. This view they have termed 'the double-threshold theory of oestrogen stimulation'. That the stimulatory range—even in the dairy animal—is small, probably explains why a similarly induced lactogenesis has only rarely been observed in laboratory mammals.

A brief review of attempts to determine directly the changing levels of lactogenic hormone secretion in response to oestrogen administration leads to the conclusion that no fully satisfactory experiments have yet been performed.

A parallel instance of the stimulatory action of oestrogens upon the secretion of a pituitary hormone is afforded by the well-known 'Hohlweg effect'¹—an enhanced output of the luteinizing hormone

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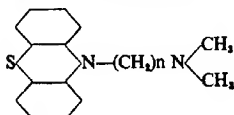
in response to an exogenous oestrogen application; but the literature suggests further that, given the correct conditions, the secretion of other pituitary hormones, too, may well illustrate the principle of the 'double-threshold' theory. This possibility is considered.

In its implications the theory is in good accord with the deductions made on cytological grounds by Severinghaus³ from his studies on the effect of oestrogens on the acidophils and basophils of the pituitary gland, and it is suggested that the phenomenon of oestrogenic stimulation may be one of general application to the secretion of pituitary hormones and of fundamental physiological significance.

¹ Various authors, *J. Endocrinol.* 4, no. 1 (1944). ² Folley, S. J., Scott-Watson, H. M., and Bottomley, A. C., *J. Dairy Res.* 12, 241 (1941). ³ Severinghaus, A. E., *Physiol. Rev.* 17, 556 (1937).

HALPERN, B. N. (Paris). Recherches sur les propriétés antihistaminiques et antianaphylactiques des dérivés de la thiodiphénylamine.

Nous venons de découvrir parmi les dérivés de la thiodiphénylamine des corps doués d'une activité antihistaminique et antianaphylactique très puissante. Leur formule générale peut s'écrire:



Parmi eux, le N-diméthylamino-éthyl-thiodiphénylamine (3015 RP), le N-diméthylamino-2-propyl-1-méthoxy-thiodiphénylamine (3299 RP) et le N-diméthylamino-2-propyl-1-thiodiphénylamine (3277 RP) paraissent particulièrement intéressants. Ils protègent le cobaye respectivement contre 500, 400 et 1.500 doses léthales d'histamine. Ils inhibent l'effet de l'histamine sur les organes lisses à des concentrations inférieures à celles de l'histamine utilisée. Injectés préalablement au cobaye à des doses de 0 mg. 5 à 2 mg./kg., ces corps protègent le cobaye contre les dyspnées asthmatiformes graves que détermine l'inhalation d'aérosols d'histamine. A ce point de vue, le 3277 RP se distingue par une durée d'action particulièrement prolongée. Ils s'opposent à l'effet de l'histamine sur la pression

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systémique chez le lapin, le chat et le chien. Ils annulent l'effet de l'histamine sur la circulation pulmonaire. Ces corps sont incapables d'inhiber l'action de l'histamine sur les sécrétions externes. La disparité entre l'extraordinaire pouvoir antitoxique général des dérivés de la thiodiphénylamine vis-à-vis de l'histamine et leur inefficacité sur l'effet sécrétoire gastrique, permet d'expliquer l'apparition chez les animaux ayant reçu plus de 100 doses léthales d'histamine, d'ulcère et de perforations gastriques dans des délais assez brefs. Le 3277 RP protège le cobaye contre le choc anaphylactique à la dose de 0 mgr. 10.

Ces corps empêchent l'apparition de l'éosinophilie pulmonaire coutumière chez le cobaye ayant survécu à un choc anaphylactique. Chez l'homme, ils empêchent la production de la triple réaction de Lewis à l'histamine et la réaction de Prausnitz-Küstner.

HANSEN, A. T. (Copenhagen). On the construction of an electric condenser manometer for measuring pressure and pressure variations in the human body.

The pressure measurement is based on the influence of a pressure upon an electric condenser. The principle has been described by *Buchthal* and *Warburg* (1943) and by *Lilly* (1942) and *Joseph Frommer* (1943) independently of each other.

The electric parts, a high-frequency aggregate and a D.C. amplifier, are in the main the same as used by the first mentioned authors. Various kinds of oscillographs may be used as recording instruments. The following demands were made on the preliminary qualities of the manometer: (1) length of the needle 5-7 cm.; (2) outside diameter as small as the needed rigidity would allow, i.e. about 0.4-0.5 mm. with the corresponding bore about 0.22 mm.; (3) damped natural frequency 50-100 cps., degree of damping 0.7; (4) sterilization and air free filling by boiling; (5) free mobility of the manometer in relation to the registration instruments; (6) a construction that allowed the properties of the manometer to be calculated in advance and the instrument to be easily reproduced.

The calculations of the dimensions of the manometer were based on the theory of manometers worked out by *Warburg* and the author

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as were the formulae expressing the behaviour of circular, elastic membranes clamped at the edge.

The manometer is made of chromium-plated brass. The fixed electrode is attached to a plate of insulating material. The pressure sensitive electrode, a circular phosphor-bronze plate, of thickness 0.4 mm. area 1 cm.², forms the end wall of the chamber, which is filled with liquid when in use. Two three-way cocks connect the chamber with the outer air, a pressure generating system and a needle. The total volume of the chamber and the cocks is 1 cc. The volume elasticity coefficient is 4×10^9 dyne/cm.⁴. With a needle of length 6 cm. and bore 0.22 mm. the damped natural frequency is 80 cps., the degree of damping 0.7. The sensitivity depends on the electric system and is variable. The manometer and the amplifier is connected by a 1.25 cm. long, low capacity cable, which is freely movable and flexible.

Recordings from various arteries and heart cavities will be demonstrated.

HARTRIDGE, H. (London). The photoreceptors of the human fovea.

In a recent paper on "The Visual Perception of Fine Detail"¹ a description has been given of the changes in hue which test objects undergo as the visual angle is progressively reduced. These changes, which involve all parts of the visible spectrum, range from full colour vision on the one hand to colourless foveal vision on the other. Several intermediate stages may be recognized. At one of these both yellow and blue have lost all colour and have been replaced by shades of grey, but red and green have suffered no apparent loss.

An attempt was made, with incomplete success, to account for the loss of colour suffered by yellow, and its retention by red and green, on the three-colour theory of *Thomas Young*; but the colour changes were found to be more compatible with the hypothesis that human vision resembles superficially that found by *Granit*, by the use of micro-electrodes, in being polychromatic. Other experimental observations made by the author appeared to be more in favour of the existence in the fovea of several different types of colour receptor,

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rather than three only. Thus there were found to be several different fixation points for the spectral colours; and several different subjective colours were observed when a narrow exploratory beam of white light was caused to move slowly over the retina, by means of a microstimulator, in the presence of suitable conditioning coloured stimuli. These three pieces of evidence were difficult to account for in a satisfactory manner on the three-colour theory, and this difficulty led to an examination of the evidence of other phases of colour vision: hue and saturation discrimination, and the luminosity curves—both for normal and for partially colour-blind subjects—the retinal direction effect, the results of adaptation to spectral colours, the colour vision of the peripheral retina, &c. This examination, which is still in progress, appears at present to be more in favour of the polychromatic than of the three-colour theory.

¹ *Phil. Trans. B.* **232**, 519–671 (1947).

STOPPANI, A. O. M. (Buenos Aires). **Indole-3-acetate metabolism.**

Indole-3-acetic acid has been found and isolated in animal fluids and tissues by previous workers. A specific photometric method that determines 1 γ indole-3-acetic (IA) in a 3 g sample has been worked out. With this method has been found that IA injected in the blood is removed by kidneys and liver. Those organs destroy IA by oxidation as can be shown in experiments with tissue slices. Indole-3-ethylamine, indole-3-pyruvate and tryptophane are partially transformed in IA either *in vitro* or *in vivo*. Negative results were obtained with indole-3-propionate and skatol. The role of IA in tryptophane metabolism is discussed.

WARBURG, E., and HANSEN, A. T. (Copenhagen). **The general theory of liquid-filled manometers and its application to a new electric condenser manometer.**

Since Frank exposed his theory on manometers for measuring blood pressure at the beginning of this century, no further theoretical advance has been published.

The possibilities opened by the new electric manometers rendered

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it necessary to develop the existing theory further in order to calculate the dimensions of the manometer for different purposes, when undistorted recordings are demanded.

As is well known from the mathematics of physics the behaviour of free oscillating systems depends on the mass, the frictional force and the directional force.

Frank used rubber membranes and tubes of such calibres that Poiseuille's law did not hold good, wherefore he did not succeed in calculating the value of the frictional force in the equation.

The theory presented here gives the hemodynamic interpretation of the damping constant in the homogeneous equation of oscillations besides the interpretation of the other constants given by *Frank*.

The difficulties met with in overdamped oscillations concerning the experimental determination of the dynamic constants have been overcome by means of a calculating system, which was originally worked out for the string galvanometer by *Warburg*, and which is to be published on another occasion.

The theory has been checked experimentally, making use of transient pressure actions upon the manometer. The theory and the experiments agreed well.

WINTON, F. R. (London). The resistance to blood flow in the kidney.

The unique property of the kidney in exhibiting increased resistance to blood flow at increased arterial pressures was demonstrated on the heart-lung-kidney preparation and tentatively attributed to increased glomerular filtration and consequent increased viscosity of blood flowing in the vasa efferentia (*Winton*, 1932).⁵ Observations (*Whittaker* and *Winton*, 1933)* on the change of viscosity with corpuscular concentration of blood flowing in dogs' hindlimbs enabled calculations to be made of the quantity of glomerular filtrate at a given arterial pressure required to produce the observed increase in the resistance to blood flow, and it was found (*Winton*, 1937) that the filtration rate so calculated was about threefold the creatinine clearance simultaneously measured under conditions in which the creatinine and inulin clearances are known to be identical

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(Shannon and Winton, 1940).¹ Selkurt (1946)² recently confirmed that the increased resistance to flow at increased blood pressure was characteristic of the kidney, whether innervated or denervated, in the anaesthetized dog, and adopted the above hypothesis of increased viscosity of blood without commenting on the quantitative discrepancy between its consequences and the creatinine clearance.

Further analysis of the resistance to blood flow has been performed on pump-lung-kidney preparation of the dog. At body temperature the resistance increases from a pressure of 50 mm. Hg. to a flat maximum of about 130 mm. and then declines slowly. The kidney perfused with cold blood (4–12° C.) still exhibits the phenomenon of increased resistance, the blood pressure-flow curve being linear from 70 to 130 mm. Hg. Scaled to a standard flow of 100 c.c. per min. at 120 mm. Hg. the resistance over the range of 80 to 180 mm. Hg. averages about 4 c.c. per min. per 10 mm. rise in arterial pressure at body temperature, and 7 c.c. per in. per 10 mm. in the cold (4–12° C.). Scaled similarly, the resistance at body temperature in a glass tube would be 8.3 and in the hindlimb 10 c.c. per min. per 10 mm. The lower resistance in the cold than in the warm kidney may be due to the lower filtration rate in the cold (even after correction for blood flow), shown by Bickford and Winton (1937).¹ Nevertheless, if glomerular filtration rate be varied experimentally by temperature, diuretics, poisons, or ureter pressure, a scrutiny of the resistances to blood flow and of creatinine clearances, simultaneously measured at the same arterial pressure, does not reveal any simple relation between them. Since intrarenal pressure does not increase notably with arterial pressure in either warm or cold kidneys (Winton, 1936)⁶ the mechanism of the resistance to blood-flow in the kidney has not yet been satisfactorily explained.

¹ Bickford, R. G., and Winton, F. R., *J. Physiol.* **89**, 198 (1937). ² Selkurt, E. E., *Amer. J. Physiol.* **147**, 537 (1946).

³ Shannon, J. A., and Winton, F. R., *J. Physiol.* **98**, 97 (1940). ⁴ Whittaker, S. R. F., and Winton, F. R., *J. Physiol.* **78**, 339 (1933).

⁵ Winton, F. R., *Trans. XIVth Congress Internaz. di Fisiol.*, p. 264 (1932). ⁶ Winton, F. R., *J. Physiol.* **87**, 18P (1936).

ZIMMERMANN, G. (Zurich). The influence of drying on the biological value of nitrogenous substances and on the level of oxydation which they produce in the metabolism of albino rats.

The home-production of concentrated fodder in Switzerland had to be increased during war-time. The furtherance of artificial (electric) grass drying served this purpose. The quality of dried grass from young albuminous plants which comes into question, primarily as concentrated fodder, varies according to the conditions in the drying process.

A comparison was therefore made with alfalfa leaves between the biological value (B.V.) (that percentage of nitrogenous substances in the fodder which is retained out of 100 parts of such absorbed substances) and the level of oxydation (measured by the C/N quotient of urine).

Alfalfa leaves were dried to 70° C., thoroughly mixed and divided into 10 parts. To one part was given no further treatment (control). Each of the remaining nine was respectively dried further under the following conditions:—

Temperature	130° C.	150° C.	170° C.
Time in minutes	15	15	15
	30	30	30
	60	60	60

After grinding, the alfalfa leaves were supplemented to such a degree as to satisfy the caloric and all other needs of the experimental animal. 10% of the calories in the dry matter of every 'N-Fodder' belonged to the only source of nitrogen, i.e. alfalfa leaves. Every animal received the same quantity of dry matter (7.5 gm. per day) also in the 'N-free Fodder' and in it the same amount of calories, fibre and essential supplements.

Plan of Experiments:

Exp. 1. (a) N-Fodder	Exp. 4. (a) N-Fodder
• (b) Standard period ¹	(b) Standard period ¹
• „ 2. (a) N-free Fodder	„ 5. (a) N-free Fodder
• (b) Standard period ²	(b) Standard period ²

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Exp. 3. (a) N-Fodder

(b) Standard period¹

Exp. 6. (a) N-Fodder

(b) Standard period¹

¹ Mixture rich in dried egg.

² (I) + grains in order to prevent damage to teeth.

Results:

An increase of the drying temperature by 1° C. lowers, in the tested range of temperature and time, the B.V., on an average, by 0.38 units. A prolongation of the drying time by 1 min. reduces the B.V., in the range of regression, by 0.1 units, on an average.

The value of the urine quotient C/N is not influenced by the temperature and duration of the drying process. Its average is 2.0364 ± 0.051 . The level of oxydation in the metabolism is not measurably influenced by the altered quality of the nitrogenous substance of the fodder, in consequence of the different conditions in the drying process.

The simple determination of the level of oxydation cannot replace the complicated determination of the B.V. because there is neither a physiologically nor a statistically significant relation between these measures.

In spite of the well-founded critique of *Schoenheimer* and others the significance of the determination of the B.V. as an informative scale of comparison is not to be denied.

BÁRÁNY, ERNST H. (Uppsala). Intra-ocular pressure and flow of aqueous humour.

A study in rabbits of the exchange of the sodium of the aqueous at different intra-ocular pressures has shown that the rate of volume flow of aqueous is remarkably little influenced by the change in intra-ocular pressure (Bárdny, 1947).¹ *Friedenwald* and *Pierce*² (1932) inserted a cannula in the anterior chamber of dogs and determined the rate of inflow of saline through the cannula as a function of pressure. They found a plateau, where flow changed very little with pressure, situated some 3–10 mm. Hg. above the intra-ocular pressure of the deeply anaesthetized dogs. I have repeated their experiment in a highly trained dog where it could be performed with only slight sedation under topical anaesthesia. The

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intra-ocular pressure of the unanaesthetized dog fell within the region of the plateau.

These experiments in two species with completely different methods show that the rate of flow of aqueous is somehow stabilized at its physiological level. Considering the function of the aqueous as a nutrient medium for the lens this would seem to be a useful arrangement. If too slow, the circulation of the aqueous might well become a limiting factor for the metabolism of the lens.

Concerning the actual mechanism of the stabilization, nothing definite is known. Possibly the mechanism of the filtering angle might be responsible for at least part of the effect. If, as seems very probable, osmotic forces participate in the removal of the aqueous, one would expect dilution by the aqueous of the contents of the recipient vessels to be important. A decrease in flow of aqueous would cause decreased dilution and increased osmotic attraction. This would tend to keep up the rate of flow of aqueous.

¹ Bárány, E. H., *Brit. Journ. Ophthalm.*, 31, 160 (1947).

² Friedenwald,

J. S., and Pierce, H. F., *Arch. of Ophthalm.*, 8, 9 (1932).

BLISS, ALFRED F. (Boston). The relation of vertebrate and invertebrate visual systems.

Vertebrate visual pigments consist of complex proteins which bleach in the light with the release of yellow lipides, one of which is a previously unknown carotenoid, named retinene by Wald. Retinene is subsequently converted by the retina to vitamin A. In the dark the vitamin A is utilized to regenerate the visual pigment. The bleaching of vertebrate visual pigments such as rhodopsin is so striking that it is generally considered a necessary property of a visual pigment.

It has, however, been found (Bliss, *J. Gen. Physiol.*, 1943) that the retina of the squid and certain crabs contain large quantities of a red pigment which becomes sensitive to light in the presence of dilute formalin, and bleaches with the release of retinene. This pigment has recently been purified (Bliss, *Biol. Bull.*, 1946) and found to exhibit an absorption spectrum identical with that of rhodopsin, but to be unbleached by light. Because of this distinctive property it is proposed that the retinal pigment of the squid be given a specific name, cephalopsin.

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Present evidence leads to the view that the primary function of both vertebrate and invertebrate visual pigments consists of the absorption of radiant energy. An activated molecule thus formed probably transfers this energy to the metabolic mechanism of the sensory cell by unknown reactions.

The release of unstable lipides by bleaching rhodopsin affords an approach for the study of the visual cycle. Studies in this laboratory have led to the following scheme for the bleaching course of rhodopsin. The first known intermediate product of bleaching, called transient orange by Lythgoe, is converted in a few minutes at room temperature to indicator yellow, a colorimetric pH indicator, the acid tautomer of which is unstable in acid solution and forms retinene.

In frog retinas or fresh neutral digitonin solution, bleaching follows a different course due to the presence of a labile factor which converts either indicator yellow or retinene to vitamin A in about 20 minutes at 25° C. The factor is destroyed by the proteolytic enzyme, trypsin, and by standing for 3 hours at 25° C. It is active between pH 5.5 and 8.0, with a maximum at 6.7.

The retina of the squid yields indicator yellow, when treated with polar organic solvents such as acetone, which releases this lipide from rhodopsin as well. This is further evidence for the basic similarity of the visual systems of the cephalopsin and rhodopsin type.

BRUN, C., HILDEN, T., and RAASCHOU, F. (Copenhagen). On the effects of mersalyl on the kidney function.

The following three partial functions of the kidney have been determined:

1. The *glomerular filtration rate*. (Inulin clearance.)
2. The *renal tubular mass*. (Diodrast-T_m.)
3. The *renal blood flow*. (Diodrast-clearance.)

During the experiments we have induced slowly rising plasma-concentrations of diodrast, so that we have been able to determine:

4. The plasma concentration of diodrast, where the diodrast clearance begins to fall in consequence of reduced plasma extraction. (*The self-depression limit.*)

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5. The lowest plasma concentration of diodrast, where the tubular secretion is maximal. (*The saturation-limit.*)

6. The degree of *dispersion* of the function of the nephrons.

We tried to alter the maximal tubular secretion in order to observe the effect on the two other functions; our choice fell naturally upon mersalyl, whose effect consist of an inhibition of the water and chloride reabsorption in the tubules.

On the same normal experimental persons, partly without and partly under the influence of mersalyl, we determined the inulin, urea and diodrast clearances, as well as the tubular diodrast secretion, inducing a slowly increasing diodrast concentration, while keeping the inulin concentration constant. Fifteen minutes before the beginning of the first period, we injected 15–20 cg. mersalyl i.v., and throughout the experiment we administered a sustaining dose of 15–20 cg. mersalyl by slow intravenous infusion during ca. 3 hours.

Under the influence of mersalyl the following results were obtained:

1. The *inulin- and urea clearance* do not alter.
2. The *diodrast- T_m* (and para-amino-hippuric acid T_m) was reduced to about 25–40% of the values in the normal experiments.
3. The *diodrast clearance* at very low plasma concentrations (below 1 mg.%) is normal, showing that renal blood flow is not altered.
4. The *self-depression limit* is found to be reduced considerably (from ca. 5–10 mg.% to ca. 1 mg.%).
5. The *saturation limit* moves only slightly downwards.
6. The range of variation of the tubular function is much greater than for the normal kidney.

BRUN, C., HILDEN, T., and RAASCHOU, F. (Copenhagen). **On the determination of diodrast clearance at rapidly decreasing and increasing plasma concentrations.**

During the determination of diodrast clearance on spontaneously falling plasma concentrations after a single intravenous diodrast injection we observed unexpectedly low clearance values—in spite of plasma concentrations well below the self depression limit—as

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compared with corresponding clearances determined on constant plasma diodrast concentrations.

As some authors are using falling diodrast plasma concentrations as a routine method for determining the diodrast clearance, we found it necessary to explore this phenomenon in detail.

In 15 experiments on spontaneously falling plasma concentrations 11 showed obviously too low clearance values and the other 4 experiments gave normal or uncertain results.

The following explanation may be proposed: If the arterial blood diodrast concentration is constantly lower than the cubital venous blood concentration during a spontaneous fall of concentration, the usual (venous) diodrast clearance will be calculated lower than the real (arterial) diodrast clearance.

This possibility has been confirmed in more experiments by simultaneous determination of diodrast concentration in arterial and in venous blood.

The observed differences in the arterial and venous blood concentrations are explained in the following manner: In the right side of the heart the renal venous blood—more or less deprived of diodrast—is mixed with the venous blood from all other parts of the organism. Consequently the arterial blood will have a lower concentration of diodrast than the extrarenal venous blood (e.g. cubital) at the same time.

The difference is dependent on the diodrast extraction in the kidney and the proportion between renal blood flow and cardiac output.

On rising plasma concentrations of diodrast we found just the opposite phenomenon: the diodrast clearance is too high, due to higher blood concentrations in arterial than in venous blood.

As a consequence of this observation we must conclude that diodrast clearance cannot be determined on spontaneously falling blood concentrations after a single intravenous injection. The correct procedure will be to maintain a constant or nearly constant diodrast blood concentration.

EDHOLM, O. G., and HOWARTH, S. (London). The effect of haemorrhage on the peripheral circulation in man.

When the venous filling pressure of the heart is reduced by venesection, cardiac output decreases, but blood pressure is maintained. Arteriolar constriction must therefore occur. The site of this constriction has been investigated by studying forearm bloodflow.

The effects of a venesection of one litre were studied in normal adults. Forearm bloodflow was measured by the Lewis-Grant plethysmograph with modifications previously described by *Barcroft* and *Edholm*. A waterbath temperature of 34.0° C. was employed. Blood pressure readings and heart rates were recorded at frequent intervals. The bloodflow was recorded before, during and after the venesection, and was followed subsequently at intervals for periods up to 20 hours. In some subjects fainting resulted, and bleeding was stopped even if the total amount of blood withdrawn was considerably less than 1,000 ml. The remaining subjects showed no symptoms. Forearm bloodflow was followed in both series of cases.

HOEFER, P. F. A., HOFF, H. H., and PLUVINAGE, R. I. L. (New York). The significance of abnormal cortical potentials occurring in 'larval' seizures and those persisting after the control of seizures.

The starting point of this study is the common observation that bursts of abnormal cortical potentials such as the synchronous spike-and-wave pattern recorded during clinical attacks of petit mal are frequently found in the inter-seizure records of the same patients. This activity is also seen in the records of patients who suffer from other forms of idiopathic epilepsy and also in close relatives of patients, though these subjects never had fits. Other abnormal patterns similarly noted are synchronous bursts of slow waves without the spike component or of spikes alone. One or all of these types of larval seizure activity were found to persist for up to three years, especially in response to over-ventilation, in thirty-one of forty patients in whom grand mal or petit mal attacks were completely controlled by medication or else had ceased spontaneously.

Spike-and-wave groups are recorded from the exposed cortex

in laboratory animals during induced convulsive seizures (Hoefer and Pool)² and, without convulsive movement in response to electrical stimulation of midline structures (Hursh, Jasper, and Penfield).^{3, 4} Non-paroxysmal cortical activity originating in layer V (Murphy and Dusser de Barenne)⁵ is conducted in the pyramids (Adrian and Moruzzi, Hoefer and Pool)^{1, 2} and in the corpus callosum (Hoefer and Pool)² but is subliminal for the lower motor neurone and does not fire cells in the opposite cortex. In deep anesthesia and in states of anoxia the cortical activity may persist while the conducted pyramidal activity disappears (Adrian and Moruzzi).¹

These varied observations seem to indicate the existence of complicated neuronal mechanisms required for the actual production of fits. Areas in which potentially paroxysmal activity arises are at times but not always capable of discharging over neuronal chains connecting with the motor system activated in the convulsive seizure. Another system is presumably implicated in the production of unconsciousness, which is associated with the convulsive seizure and is the principal feature of the petit mal attack. The site of origin and the pattern of the primary discharge may be relatively unimportant except for the actual clinical type of attack. It is reasonable to assume from electro-encephalographic evidence that in most instances the discharge arises in or reaches the cortex. A process of the nature of facilitation may be required to complete the actual fit. Drug treatment might interrupt the neuronal chain without abolishing the primary discharge.

¹ Adrian, E. D., and Moruzzi, G., 'Impulses in the Pyramidal Tract', *J. Physiol.* 97, 153 (1939). ² Hoefer, P. F. A., and Pool, J. L., 'Conduction of Cortical Impulses and Motor Management of Convulsive Seizures', *Arch. Neurol. and Psychiat.* 50, 381-400 (October, 1943). ³ Hursh, J. B., 'Origin of the Spike and Wave Pattern of Petit Mal Epilepsy', *Arch. Neurol. and Psychiat.* 53, 274 (April, 1945). ⁴ Jasper, H. H., and Penfield, W., *Proceedings of the Assoc. Res. Nerv. and Ment. Dis.* (1946). ⁵ Murphy, J. P., and Dusser de Barenne, J. G., 'Thermocoagulation of Motor Cortex Exclusive of Its Sixth Layer', *J. Neurophysiol.* 4, 147 (1941).

HOWARTH, S., and SHARPEY-SCHAFER, E. P. (London). The effect of raising venous pressure on total and peripheral bloodflow in man.

The effects of raising the venous filling pressure of the heart by rapid infusion of normal saline were studied in adults. Forearm blood-

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flow was measured by the Lewis-Grant plethysmograph (*Barcroft and Edholm*, 1943). Right auricular pressure and cardiac output were determined by cardiac catheterisation (*McMichael and Sharpey-Schafer*, 1944).

When right auricular pressure was raised above sternal angle level, the bloodflow decreased, which, together with a rise in blood pressure, indicated constriction in the forearm vessels. This occurred both with a rising cardiac output and when the heart was overloaded. Acceleration of the heart by the Bainbridge reflex did not always occur.

Confirmatory evidence of this reflex may be obtained in subjects with heart disease with high right auricular pressures, in whom forearm bloodflow is low, and in subjects showing Cheyne-Stokes respiration in whom cyclical changes occur in blood pressure and in forearm bloodflow.

KAISER, L. (Amsterdam). **Sociophysiology.**

To many physiologists the physiology of man seems a far purpose, which will be reached perhaps after some more centuries of frog and rabbit work. This is a scientific point of view, but on the other hand it may be asked whether the problems of exquisite human physiology may wait so long.

Physiology deals with vegetative and animal functions; specific human functions are not considered, as if humanization only concerned the psychic functions, leaving somatic life as it appears in the higher mammals.

Nevertheless the influence of social life on both somatic and psychic functions is well known. Civilization, urbanization, domestication are forces that urge the physiological functions of man into special forms. The lower senses are deprived of stimuli, whereas excitations of the higher senses accumulate. Motorics are inhibited from the earliest childhood. Reflex functions are activated perpetually. Integration of the function of the central nervous system has been lost to a large degree, cortical functions acting separately in many cases.

The controversy between the demands of society and those of the biological individual has been treated in several philosophical systems, but as physiology developed it did not partake in the

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research into this problem. Physiological chemistry, on the one side linked to chemistry and physical chemistry, on the other hand recognized the necessity of dealing with the problems of feeding together with economical and social sciences.

Physiological physics seemed almost unaware of the problems in its own territory, though society demands data in the field. Various groups of workers in examinations for life insurance, sports, employment, marriage, tried to answer the demands, but the vast material gathered seems too incoherent to yield composing and comparing, which would give the norms wanted.

Perhaps it will be possible to start a co-operation between physiologists in various countries working in the field of what may be called sociophysiology. I know there are physiologists of this kind spread over the world and I hope they will propagate the above purpose on the occasion of the Seventeenth International Physiological Congress.

KAPELLER-ADLER, R. (Edinburgh). Histamine metabolism in pregnancy.

In continuation of earlier work the histamine-content as well as the histaminase activity were determined in the blood and serum of 130 women with normal and toxæmic pregnancy in various stages of gestation. Barsoum and Gaddum's method, as modified by Code, was used for the estimation of histamine (calculated as base), and the identification of this substance was confirmed in a number of cases by tests with the antihistamine drug neoantergan. A modification of Zeller's colorimetric indigo-method was applied to the serum as a test for histaminase.

In nine *non-pregnant* persons no histaminase was detected in the serum and the mean blood-histamine was 38 ± 6 (standard error of mean) $\mu\text{g.}$ per litre. In *normal pregnancy* the tests for histaminase confirmed the results obtained by other methods (cf. Ahlmark, 1944). The activity increased in the third month, reached a peak about the seventh month, decreased slightly towards the end of pregnancy and fell rapidly in the puerperium or after abortion. The mean blood-histamine was $40 \pm 2 \mu\text{g./l.}$ (39 cases.)

In *pre-eclamptic toxæmia* various abnormalities were seen. In

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33 mild cases the serum-histaminase was not very different from that of normal pregnant women, but the blood histamine was high ($69.5 \pm 4.2 \mu\text{g./l.}$). In some cases, a fall of blood-histamine was associated with a deterioration of the clinical condition.

In 23 women with moderate or severe toxæmia the serum-histaminase was generally less than in normal pregnancy. The average blood-histamine in this series was high, but it was comparatively low in the more severe cases, and in normal labour. (15 cases.)

These results suggested that, in toxæmia and in labour, the histamine might shift from the cells into the tissue fluids. In a further series of 36 pregnant women, histamine was therefore estimated separately in the blood cells and in the plasma. The results for plasma were particularly striking. In 15 normal pregnancies the plasma-histamine was generally so low as to be scarcely detectable. (Mean $5.5 \pm 2.7 \mu\text{g./l.}$) In 12 toxæmic cases the mean value was significantly higher ($25.8 \pm 9.2 \mu\text{g./l.}$). In normal labour it was also high ($26.3 \pm 7.5 \mu\text{g./l.}$) (9 cases).

The investigations are being continued; the significance of the results will be discussed.

McMICHAEL, J., and SHARPEY-SCHAFER, E. P. (London). The influence of heart rate in regulation of cardiac output in man.

The effect of heart rate changes on cardiac output in man have been studied by the method of cardiac catheterisation. The resting cardiac output in normal subjects bears a relationship to the heart rate and both are more labile in younger subjects. 2 mg. atropine were injected intravenously into normal subjects to produce acceleration. The increase in heart rate was accompanied by a fall in right auricular pressure, so that in some subjects the initial increase in cardiac output from acceleration was followed by a decrease from the fall of venous filling pressure.

Cases of heart failure were also given intravenous atropine. A fall of venous pressure in these cases produces an increase in cardiac output. Some subjects showed little change in cardiac output in spite of conspicuous increase in heart rate. Spontaneous variations

in the heart rate in normal and other subjects have been observed. Cardiac output may reach high levels in tachycardia from emotional causes.

MARSHALL, R. A., and PHILLIPSON, A. T. (Cambridge). The relation between the proportions of acetic and propionic acids passing from the rumen of sheep.

The mixture of acids present in the rumen of sheep consists of acetic, propionic and butyric, with possibly a fourth unidentified acid: of these, acetic predominates, forming from 55% to 75% of the total. Comparison of the distillation curves of the mixture of volatile acids present in the rumen with that present in the blood draining the rumen suggests that the proportion of acetic in the blood is greater than that in the rumen (*Barcroft, McAnally, and Phillipson, 1944*):¹ further studies of the behaviour of mixtures of the three acids introduced into the empty rumen show that at a pH when acid anion only is present, the smaller molecules disappear more rapidly, but the absorption of free acid when the pH is reduced, in contrast to acid anion, increases with molecular size (*Danielli, et al., 1945*).² Similar results obtained by *Grey (1947)*³ led him to suggest that the proportion of acetic to propionic acid in the rumen under natural feeding conditions may be the result of preferential absorption of propionic acid rather than of greater production of acetic acid, so that the sheep actually obtains more propionic acid than has hitherto been supposed (*Grey, 1947*).⁴

Comparison of the mixture of acids found in the rumen of sheep taken from pasture, or recently fed with hay, with that leaving the rumen in the blood or in the digesta does not support this contention. Chromatographic partition of the acids obtained from distillates of large samples of blood draining the rumen, using the technique described by *Elsden (1946)*,⁵ proves that the proportion of acetic to propionic acid is greater in the blood than in the mixture present in the rumen. Partition of the acids in the abomasal digesta fails to show any significant dissimilarity from the mixture present in the rumen. The validity, therefore, of the hypothesis depends upon the amount of propionic acid carried from the rumen in the lymphatic system, and this needs investigation.

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- ¹ Barcroft, J., McAnally, R. A., and Phillipson, A. T., *J. Exp. Biol.* 20, 120 (1944). ² Danielli, J. F., Hitchcock, M. W. S., Marshall, R. A., and Phillipson, A. T., *J. Exp. Biol.* 22, 75 (1945). ³ Elsdon, S. R., *Biochem. J.* 40, 252 (1946). ⁴ Grey, F. V., *J. Exp. Biol.* (1947) (in press).

ROBSON, J. M., and HÖHN, E. O. (London). Antagonisms of steroid hormones.

The action of oestrogens on the vaginal epithelium, which results in proliferation and cornification, can be antagonised by progesterone, testosterone, methyl testosterone, and by desoxycortone. One possibility is that there is an antagonism between these substances and the oestrogen, acting directly on the cells of the vaginal epithelium. If this is the case it would be expected that the direct application of the antagonists to the vagina would inhibit the action of oestrogen in doses smaller than are necessary to produce this effect when they are given systemically. This was not found to be the case. With progesterone and desoxycortone doses similar to those effective subcutaneously had to be given intravaginally in order to inhibit the action of oestradiol. With methyl testosterone the result was even more unexpected: 20 μ g. of this substance, given subcutaneously, produces an appreciable inhibition of the action of oestradiol and with 50 μ g. the inhibition is very marked. But when methyl testosterone was given intravaginally in doses of 2,000 μ g. it produced only a slight, if any, inhibition of the action of oestradiol. In order to make sure that the methyl testosterone was actually absorbed from its site of application, it was administered to groups of ovariectomised mice, both by the vaginal and the subcutaneous routes, and the effect on the growth of the vagina and uterus compared. The results showed clearly that methyl testosterone is well absorbed when given intravaginally.

In the uterine endometrium of ovariectomised rabbits a direct antagonism between progesterone and oestradiol could be demonstrated. It was found that the local administration of progesterone, in crystalline form or as a progesterone-cholesterol fused mixture, produced a progestational effect with doses of progesterone as small as 1 μ g. Indeed, the reaction has a fairly clear-cut threshold value and it is hoped to develop it into a method of assay for progesterone.

*When oestradiol is given locally with progesterone, the endo-

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metrial reaction can be completely inhibited; the antagonistic effect is a local one since a similar dose of progesterone implanted into another site in the same uterus produces its full progestational effect. Complete suppression of the progesterone effect was obtained with an oestradiol/progesterone dosage ratio similar to that which is effective when both substances are administered systemically. The actual effective antagonising dose of oestradiol is of course much smaller than that needed to antagonise the minimum effective dose of progesterone when both substances are given systemically.

WYSS, O. A. M., and OBERHOLZER, R. J. H. (Geneva). **The vagal reflex pathways through the respiratory centre.**

Respiratory reflexes elicited by electrical stimulation of the afferent vagus nerve are of a more inspiratory or a more expiratory type depending upon stimulus frequency. An increase of the rate of stimuli produces a change from the inspiratory to the expiratory reaction corresponding to the physiological reflex reversal induced by progressive distention of the lungs.

By means of small localized lesions applied by high frequency coagulation at the level of the medulla oblongata either the inspiratory or the expiratory reflex component can be selectively removed. The responsible lesions lie in and around the tractus solitarius, at a somewhat higher level (2 mm.) for the expiratory and a lower level for the inspiratory effect.

From this combined physiological and anatomical study, it can be concluded that the afferent respiratory fibres of the vagus nerve enter the medulla oblongata through the upper bundles of the vagus root, join the solitary tract at about the same level and run down in this tract. They leave it again entering the adjacent grey matter especially on the medial side where they probably get in synaptic contact with internuncial neurones. At a higher level this common internuncial neurone pool is expiratory, i.e. the interneurones have an inspiratory-inhibitory action; at a lower level they are inspiratory-excitatory. Their further intracerebral pathways, inspiratory-excitatory as well as inspiratory-inhibitory, are not only directly descending to the inspiratory motoneurones, but they also are connected with the autonomous parts of the respiratory centre, the

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so-called inspiratory and expiratory half-centres located in the reticular substance. The anatomical determination of these internuncial pathways is the object of further investigation.

AJAZZI-MAUCINI, M. (Firenze). **The pharmacology of pharmacaine.**

Owing to the war, Italy has been lacking in many synthetic and natural alkaloids: morphine, cocaine, pantocaine disappeared from our market.

After long studies Dr. Valier produced the synthesis of a new alkaloid belonging to the family of novocaine in the molecule of which a butyl group has been introduced.

PHYSICAL AND CHEMICAL PROPERTIES

p-butylamino-benzoyl-diethyl-amino-ethanol hydrochloride



Pharmacaine hydrochloride is very soluble in water and the solution is neutral.

LOCAL ANAESTHETIC POWER

The experiments have been carried out with the usual technique on the rabbit's eye, applying the solutions on mucous membranes of the eye and controlling with the aid of a chronometer the corneal reflex's time of the closing of eyelids before and after the application of the solution.

RESULTS

1° After the application of a pharmacaine solution 1/100 the total anaesthesia lasts 68'

with a solution 1:1000 total anaesthesia lasts 44'

" " 1:2000 " " " 28'

" " 1:4000 " " " 16'

2° *Increasing of anaesthetic power by adding epinephrine.*

The solution of pharmacaine 1:36,000 gives a total anaesthesia of 2': by adding to this solution a drop of epinephrine hydr. 1/100 for each c.c. of pharmacaine solution the anaesthetic power lasts for 7'.

3° *Local anaesthetic power of pharmacaine compared with that of other local anaesthetics.*

A total anaesthesia of 4' has been obtained with a solution of cocaine 1:1000 and with a solution of pharmacaine 1:32,000: in

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these conditions the proportion between cocaine and pharmacaine is 1:32.

A total local anaesthesia of 14' has been obtained with a solution of pantocaine 1:4000 and with a solution of pharmacaine 1:8000: in these conditions the proportion between pantocaine and pharmacaine is 1:2.

A total local anaesthesia of 10' has been obtained with a solution of scurocaine 1:100 and with a solution of pharmacaine 1:16,000: in these conditions the proportion between scurocaine and pharmacaine is 1:160.

The experiments made on legs of frogs with Turk's method gave the same results.

The M.L.D. by intravenous injection is mg. 3.5 per Kg., the M.L.D. subcutaneously is 40 mg. per Kg., the proportion between subcutaneous and intravenous M.L.D. is 11:1.

Death is caused by paralysis of the medullary centres.

DE LA BARREDA, P., DE MOLINA, A. F., and JIMENEZ DIAZ, C. (Madrid). **The chemical regulation of the blood-pressure.**

In 110 dogs anesthetized with morphine and phenobarbital, the increase of the blood-pressure following the electrical stimulation of the central end of the sectioned trunk of both vagi has been studied.

Hypophysectomy, acute or chronic, nephrectomy, adrenalectomy, or liver exclusion, do not prevent the rise of the blood-pressure.

Treatment with ergotamine, enough to produce the *Dale* reversal phenomenon, does not prevent the pressor response. Such response is abolished by section of the spinal cord between C. IV and C. VI.

The mechanism of the pressor effect has been investigated in the following experiments:

(a) Crossed circulations.

(b) Injecting plasma of the dog taken during the maximum increase of the blood-pressure into another dog.

(c) In dogs with separated circulation through the hindlegs maintained with a perfusion system, with blood, plasma, or saline.

The results indicate that the increase of blood-pressure is produced by liberation of a pressor substance existing in the blood taken during the said increase of blood-pressure. Such substance is pro-

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duced only if the hindlegs are perfused with blood or plasma, but not when they are perfused with saline. The substance therefore is not produced only by the nervous action on the wall of the blood vessels. Its production requires the presence of blood-plasma.

Pharmacological tests have shown that the pressor substance is not similar to the known sympathin.

The volumetric effects have been taken into account.

In order to test the role of the arterial wall in this phenomenon, the following experiments have been performed. With the whole arterial tree of three series each, ten dogs' extracts have been prepared following a technique similar to that applied for preparing renin extracts of kidney. Renin has been prepared also from the kidneys of the same dogs, and hypertensinogen from its blood.

The extracts of the arterial wall do not produce any increase of the blood-pressure, but a pressor effect is produced when they are incubated with hypertensinogen, in a similar manner to that observed with our renin.

The pharmacological properties of the incubated arterial extracts are similar to the known properties of incubated renin plus hypertensinogen, including the potentiating effect of cocain.

It is concluded that the arterial wall produced a substance not identical with adrenaline or sympathin, which, acting on a substract existing in the blood-plasma, behaves similarly to the hypertensin.

The belief is put forward that renin is only a particular case of a general phenomenon originating in the whole of the vascular system.

BOURGUIGNON, G., HUMBERT, R., POLONOWSKI, M., et VERNE, J. (Paris). **Triple contraction et triple chronaxie du muscle strié normal. Différences histologiques et chimiques correspondantes.**

Deux d'entre nous avaient montré en 1936 que le muscle strié normal donnait une double contraction et qu'on trouvait deux chronaxies dont l'une était la même que celle du nerf et l'autre 80 à 100 fois plus grande.

*En remplaçant l'inscription au cylindre de Marey par l'inscription piézographique on retrouve la double contraction et souvent une contraction triple, aussi bien chez l'Homme que chez le lapin. En

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excitant et inscrivant isolément les faisceaux de rapidité différente, les temps perdus sont en moyenne de 0,02 sec. pour les faisceaux rapides, 0,04 sec. pour les faisceaux de rapidité moyenne et de 0,06 sec. pour les faisceaux les plus lents, et on trouve 3 chronaxies dont la plus petite est la même que celle du nerf, la moyenne 10 fois plus grande et la plus grande 80 à 100 fois celle du nerf.

Nous avons ensuite fait l'étude histologique et chimique des différents faisceaux prélevés isolément dans le Jumeau interne chez le chien et chez le lapin.

Chaque échantillon prélevé, dont la chronaxie a été mesurée, est coupé transversalement en deux, pour l'examen histologique et l'examen chimique.

Les faisceaux les plus rapides qui ont la plus petite chronaxie et le plus petit temps perdu sont les plus riches en phosphagène et les plus pauvres en sarcoplasma, les plus lents étant au contraire les plus pauvres en phosphagène et les plus riches en sarcoplasma. Les faisceaux de chronaxie moyenne viennent entre les deux.

Au contraire les autres éléments, phosphates acido-solubles, orthophosphates, adénosine-triphosphate, créatine, n'ont aucune variation systématique.

La richesse en sarcoplasma a été déterminée par la numération des noyaux par champ et par unité de longueur de fibre.

Voici un exemple de cette expérience sur le lapin :

Forme de la contraction	Chronaxie en 1/1000 de seconde	Histologie Nombre de noyaux		Chimie Milligrammes pour 100 gr. de tissu frais				
		Par champ	Par unité de longueur	Phos- phagène	Ph. acido- soluble	Ortho- phosphates	Adénosine- triphosphate	Créatine
Faisceau vif	00, 09	14	1	82	113	18	13	465
Faisceau moyen	00, 92	28	3 à 4	62	113	43	8	465
Faisceau lent	80, 40	42	5	31	81	37	13	465

Le muscle strié normal est donc bien composé de 3 sortes de faisceaux.

Il est permis de supposer que les faisceaux vifs sont les agents de la contraction clonique et les faisceaux lents ceux de la contraction tonique.

BOVET, DANIEL (Paris). Thérapeutique des états de choc.

La notion de choc recouvre des états cliniques d'étiologie très variées dont l'existence pose à l'expérimentateur un problème thérapeutique d'une exceptionnelle importance. L'ayant depuis 1937 (Bovet et Staub, 1937; Bovet et Walther, 1940) abordé par l'étude qui paraissait le plus aisément accessible des chocs histaminiques et allergiques, il nous a paru tentant d'en considérer d'autres aspects encore.

En mettant en œuvre une technique (Noble et Collip, 1942) qui consiste à suivre l'effet des chutes répétées d'un animal placé à l'intérieur d'un tambour circulaire tournant, nous avons constaté (Bovet, Courvoisier, et Ducrot, 1947) que le choc traumatique du rat pouvait être dans une large mesure prévenu par l'injection d'un polymère de synthèse, la polyvinylpyrrolidone, dont l'emploi a été préconisé en 1943 par Hecht et Weese dans le traitement des grandes hémorragies. Dans des conditions où l'on observe régulièrement la mort des animaux témoins, il est possible d'assurer la survie définitive de tous les animaux traités préventivement par la polyvinylpyrrolidone; le produit exerce également un effet curatif; la protection persiste 72 heures et plus.

Au cours de recherches entreprises en vue d'élucider le mécanisme de cet effet (Bovet, Ducrot, et Courvoisier, 1947) nous avons constaté l'activité de plusieurs amides. Le N-N-diéthylacétamide qui représente un des termes les plus simples de la série permet aussi de réaliser vis-à-vis de certains chocs traumatiques une protection caractéristique. L'a-pyrrolidone, qui peut être considéré comme un amide hétérocyclique, manifeste également une certaine action; il paraît possible d'attribuer à la présence de ce noyau dans la polyvinylpyrrolidone une partie des effets thérapeutiques du polymère.

BUU-HOÏ, NG. PH., BERGER, M., DAUDEL, P., and DAUDEL, R. (Paris). Radio-active bromine as a means of determining the mechanism of action of α -bromo- α . β -triphenylethylen (Y. 59).

α -Bromo- α . β -triphenylethylen (Y. 59) is a potent oestrogen, and is now being used with success for the treatment of prostatic cancer in France. The fate of this compound in living animals has been studied upon mice by means of radio-active bromine as a convenient

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tracer. Some α -bromo- α,β -triarylethylens which are not oestrogenic or are only very feebly so, have also been studied by this method, and the results thus obtained are compared with those related to Y. 59.

From these experiments, some conclusions bearing upon the mechanism of action of α -bromo- α,β -triphenylethylen and related compounds have been put forward and discussed.

CHEN, TING-I and TSAI, CHIAO (Nanking, China). **The mechanism of hemostasis in peripheral vessels.**

In the present investigation the mechanism of hemostasis in artery, vein, and capillary was studied in rabbit, frog, and toad by cutting, puncturing, crushing or pressing the vessel and observing its change under the microscope or recording it photographically. It was found that the hemostasis of the small artery in the rabbit ear consisted of two phases. The initial phase was vaso-constriction which is largely myogenic in nature because previous complete denervation of the ear vessels did not abolish the response. The constriction extended 1-1.5 mm. above and below the point of mechanical injury. It lasted 7-10 min. but might continue to as long as 30-40 min. The prolonged constriction may be due to the action of the vaso-constrictor substance liberated from the disintegrated platelets. Permanent arrest of bleeding depends upon the formation of a clot, the coagulation phase. In the dicumarolized rabbit the coagulation phase was absent so that rebleeding occurred after the constriction phase passed off.

No constriction of the mesenteric capillaries of the rabbit and frog and tail capillaries of the tadpole in response to puncturing or pressing was ever observed. The capillaries immediately closed at the point of injury primarily by the adhesion of its wall. If the wall did not adhere as a result of some incidental distracting force, bleeding took place, which was checked by blood coagulation within 30-90 seconds.

In the marginal ear vein of the rabbit and the mesenteric venules of the frog and rabbit the formation of a platelet plug inside the vessel at the point of injury was the most important mechanism of hemostasis. The plug was formed before coagulation. It was small

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at first and grew to a considerable size so as to form a white thrombus. The small platelet plug usually underwent fragmentation and washed away within 3-7 hours after the injury. However, if the plug was so large as to obstruct the entire lumen of the vessel, recanalization occurred 24-48 hours after puncturing. Unobstructed flow was re-established within 3-4 days. The adhesive property characteristic of the capillary endothelium was also detectable in the small veins of the toad's mesentery and rabbit's ear, but its significance in hemostasis is not yet fully understood.

CONSOLAZIO, W. V., FISHER, M. B., PACE, N., PECORA, L. J., PITTS, G. C., and BEHNKE, A. R. (Bethesda, Maryland).

The effects on man of prolonged exposure to high concentrations of carbon dioxide.

Exposure, for periods up to 72 hours in atmospheres of increased carbon dioxide concentration up to 5% and reduced oxygen concentration as low as 12%, did not appreciably impair the physical condition and efficiency of Naval personnel as evaluated by biochemical, physiological, and psychological tests. Minor symptoms of headache, nasal congestion, and dryness of the throat quickly disappeared when outside air was breathed. Compensatory physiologic changes were increased ventilation and circulatory rates. Concentrations of carbon dioxide much above 5% are not well tolerated and this value appears to be a limiting level for prolonged exposures. The test procedures yielded quantitative data on appreciable numbers of men under conditions that have not previously been reported upon.

DAVIDSON, J. N., LESLIE, I., and WAYMOUTH, C. (London).

The nucleoprotein content of fibroblasts in tissue culture.

Fresh explants of the 12-day chick embryo heart in plasma clot in roller tubes contain 2.2-2.5 times as much ribonucleic acid phosphorus (RNAP) as deoxyribonucleic acid phosphorus (DNAP). When such cultures are incubated for 24-48 hours in Tyrode solution alone as much as 30% of both types of nucleic acid may be lost.

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The addition of growth promoting media at this stage is followed by a rise in RNAP. The changes in DNAP are much smaller and do not appear to keep pace with the changes in RNAP, so that a rise in the RNAP:DNAP ratio occurs, at any rate in the initial stages. In the course of the 24 hours following the addition of growth-promoting media, regular fluctuations in the RNAP level may occur. The most obvious signs of 'growth' on naked-eye examination occur during the second 12 hours of this period.

FORTUYN, J. D., and JASPER, H. H. (Montreal). **Thalamic centers controlling rhythmic electrical activity of the cortex.**

Experiments on 25 cats were performed. Stimulation of the thalamus was performed by means of a Horsley-Clarke apparatus. Potentials were recorded from entire cortex including the medial surface and orbital surface by means of a 6-channel Offner chrystograph and a triple trace cathode-ray oscillograph. Not investigated was the basal part of the temporal lobe. The generalized cortical potentials were recorded during stimulation of the midline and near the lamina medullaris interna. Special effects were obtained if midline stimulation was carried out near the anterior pole of the dorso-medial nucleus, just behind the anterior nuclear group and farther frontally between the right and left antero-medial nucleus. Here general effects appeared on stimuli of low intensity. Bursts were initiated, starting in the frontal areas and successively appearing in more posterior parts of the cortex. Thus rhythmic potentials in the entire cortex were co-ordinated from a very restricted thalamic area, never more than 2 mm. in diameter.

Stimulation in the rhythm of the bursts caused 'driving' of the cortex. Anterior parts were better controlled from here than posterior cortical areas, so that different types of responses could be discriminated. The types of response (ranging from well controlled to poorly controlled) could be imitated in one and the same area by varying the intensity of the stimulus.

In several animals the form of the response obtained from stimulation of this restricted area became more complex. The most complex form was a wave-and-spike form, lasting more than 200 msec. and appearing in a regular sequence at a stimulation of

3 per second. Many features of the E.E.G. seen in petit mal could be imitated experimentally.

These experiments suggest: (1) that the co-ordination of different cortical areas are dependent on thalamic mechanisms; (2) that a similar co-ordination takes place under pathological conditions like petit mal.

The potential changes are not restricted to the cortex. Similar potentials could be recorded from the thalamus and caudate nucleus: large parts of the telencephalon take part in this phenomenon.

GUIMARÃES, J. A. (Porto). Contribution à l'étude des réactions vasomotrices chez le chien surrénalectomisé.

Nous avons étudié, avec *Lino Rodrigues*, l'influence de la surrénalectomie sur les effets vasculaires provoqués par l'excitation électrique du nerf splanchnique aussi bien que l'influence de l'adrénaline et de l'hormone cortico-surrénale sur les effets vasomoteurs déclenchés par l'excitation du splanchnique, chez le chien privé des glandes surrénales. Nous avons pu confirmer les observations de *Elliot*,¹ *Secker*,^{2, 3} *Armstrong*, *Cleghorn* et ses collaborateurs,⁴ qui ont constaté que l'intensité de la réponse à l'excitation électrique des nerfs sympathiques, après surrénalectomie, diminue graduellement jusqu'à devenir presque nulle, à mesure qu'on répète les stimulations, ce qui a été contesté par *Haterius* et *Maison*.⁵ Nous avons aussi remarqué cette diminution, dont témoigne la valeur de la pression artérielle, en excitant les nerfs splanchniques ou le tronc sympathique lombaire, et nous avons aussi constaté que, même dans l'état final de l'insuffisance surrénale, l'injection d'adrénaline provoquait encore la réaction hypertensive habituelle. L'étude des effets de l'excitation électrique des nerfs splanchniques, chez le chien totalement surrénalectomisé, après administration préalable d'adrénaline ou de l'hormone cortico-surrénale (Percorten Ciba) nous a permis d'arriver aux résultats suivants: (a) l'injection intraveineuse d'adrénaline, en doses variant de 10 à 250 gs., faite dans le cours ou à la fin de la phase de diminution de l'effet vasculaire provoqué par l'excitation électrique des nerfs splanchniques, n'a pas nettement influencé la réponse artérielle à une nouvelle excitation identique à l'antérieure; dans un petit nombre de cas, mais jamais à l'état final de l'insuffisance

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surrénale, nous avons constaté une augmentation légère et fugace de la valeur de la pression artérielle, tout à fait semblable à celle qu'on obtient chez un animal en bon état et avant l'administration de l'adrénaline quand on fait suivre une excitation du splanchnique, immédiatement après le retour de la pression sanguine à la valeur antérieure, d'une nouvelle excitation de même durée et de même intensité; (b) chez les chiens surrénalectomisés mais traités par l'hormone cortico-surrénale (Percorten Ciba, à la dose quotidienne de 1 à 2 mg. par Kg.), présentant initialement des valeurs tensionnelles normales, l'effet vasomoteur déclenché par l'excitation électrique du nerf splanchnique a diminué au fur et à mesure que nous avons répété l'excitation du nerf, pareillement à ce que nous avons déjà observé chez les animaux surrénalectomisés non traités par l'hormone corticosurrénale; (c) chez les chiens surrénalectomisés et injectés avec l'hormone cortico-surrénale, nous avons fréquemment observé que l'excitation électrique du nerf splanchnique, au lieu de l'hypertension habituelle, provoquait une hypotension qui résistait à l'atropinisation; (d) les résultats de l'influence de l'adrénaline sur les réactions vasomotrices déclenchées par la stimulation des nerfs splanchniques sont les mêmes aussi bien chez les chiens surrénalectomisés et traités par l'hormone cortico-surrénale que chez les animaux seulement surrénalectomisés.

¹ Elliot, T. R., *J. Physiol.* 31, 20P (1904). *Ibid.* 49, 38 (1914). ² Secker, J., *J. Physiol.* 89, 296 (1937). ³ Secker, J., *J. Physiol.* 94, 259 (1938). ⁴ Armstrong, C. W. J., Cleghorn, R. A., Fowler, J. L. A., and McVicar, G. A., *J. Physiol.* 96, 146 (1939). ⁵ Haterius, H. O., and Maison, G. L., *Endocrinology*, 30, 520 (1942).

GUTMANN, E. (Prague). The recovery of muscle after immediate and delayed reinnervation.

The recovery of muscle indicated by muscle fibre size, muscle weight, onset, and degree of functional recovery has been studied after immediate reinnervation following crushing, delayed reinnervation achieved by repeated crushing of the nerve, immediate and delayed reinnervation after suturing the nerve.

The spectrum of muscle fibre sizes in the M. extensor digit. of the rabbit and its changes during a period of denervation from 1-8 months has been studied. In the normal muscle there is a normal

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distribution of fibre sizes with a tendency of larger fibres to occur more often in the periphery of the muscle. During denervation the distribution of muscle fibre sizes becomes irregular, there is a steady shift to the small diameters but some fibres, especially those in the periphery, retain a large diameter. At later stages fibre size becomes more uniform and no fibres of large diameter are left. During the first period of denervation weight decreases at a quicker rate than fibre size.

After immediate reinnervation muscle fibre size is recovered to its initial size 5 months after crushing the peroneal nerve, i.e. 12 weeks after onset of functional recovery, i.e. of spreading of the toes. At the time of onset of functional recovery the mean diameter of the muscle fibres is still about 55% of the control side. During the following 12 weeks a normal distribution of muscle fibre sizes is reconstituted and increase of intramuscular collagenous tissue is made reversible.

By repeatedly crushing the peroneal nerve at monthly intervals periods of denervation from 1-8 months can be achieved. After a period of denervation of 6 to 8 months, onset of recovery of function is only slightly delayed. However, degree of recovery, expressed by the amplitude of the spreading of the toes becomes clearly worse. No normal degree of recovery is observed when reinnervation is delayed more than 6 months. Following delayed reinnervation the rate with which the amplitude of the spreading increases becomes progressively slower.

Even after a period of denervation of 6 and 8 months fibre size increases almost to normal values following reinnervation, although the mean diameter of fibre sizes after a period of denervation of 8 months is 32% of the control side. Considerable connective tissue increase due to denervation can be made reversible to a great extent by reinnervation.

Recovery of muscle fibre size after delayed reinnervation following secondary suture achieved by cross unions of tibial into peroneal nerve is much less efficient than after delayed reinnervation following crushing. This is thought to be due to the shunting of nerve fibres which occurs after suturing the nerve.

It appears that up to a period of 8 months of denervation the low degree of functional recovery following reinnervation is due in the

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first place to deficient maturation of the nerve fibres in the peripheral nerve trunk and to deficient terminal connexions, to a lesser degree to the atrophy of the muscle fibres. After longer periods of atrophy recovery of muscle fibre size is much more deficient, the degree of muscle atrophy being then apparently the main factor responsible for the low degree of functional recovery.

KAULBERSZ, J., PATTERSON, T. L., SANDWEISS, D. J., and
SALTZSTEIN, H. C. (Detroit, Mich.). **Urine extracts of
thyroidectomized dogs and gastric secretion.**

Urogastrone prepared from dogs deprived of their thyroid gland was administered intravenously to gastric fistula and pouch dogs, in order to investigate its influence on the response of the stomach to histamine. Controls with histamine alone were made on each of the test days.

Whereas urogastrone from normal dogs inhibited the total output of free HCl in 66% of experiments and the average diminution of the milliequivalents amounted to 25.7% as compared to controls, the reduction of gastric secretion produced by thyroidectomized dogs' urine extract proved to be more extensive and decisive. In 28 out of 37 studies or in 76% inhibition resulted and the average decrease of mE in per cent. as compared to controls rose to 51.

There was some difference depending on the period of the double histamine experiment, in which the extract was injected. When administered in the first period, i.e. before the control, the inhibition occurred in 21 out of 23 experiments (in the remaining 2 no significant differences in both periods were noted) and the average mE of the total output of free HCl were reduced 59.8%. In 14 experiments, in which the controls preceded the extract administration (second period), 7 inhibitions, 1 stimulation were found and the differences in the remaining 6 were not significant, the average inhibition of HCl mE amounted to 42%. Thus, the injection of the extract prior to the control gave more striking results than the opposite sequence.

Since our previous studies (*Science*, **102**, 530, 1945; *Federation Proceedings*, **5**, No. 1, 54, 1946; *Canad. Med. Assoc. Journ.* **54**, 69, 1946) showed that hypophysectomized dogs' urine extract does not

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inhibit gastric secretion after histamine injection in the majority of cases but rather increases the total output of free HCl, and that this difference is more pronounced when the extract administration precedes the control (*Federation Proceedings*, 6, No. 1, 140, 1947), thus a comparison of the above findings indicates that the thyroid gland may have some antagonistic function to the pituitary in regard to urogastrone production.

LAKI, KÁLMÁN (Budapest, Hungary). **Transition of fibrinogen to fibrin.**

The clotting of fibrinogen depends on pH. At about pH 5, 1 fibrinogen does not clot at all. It can be shown, however, that thrombin plays its role even at this pH, because after a certain incubation period, depending on the quantity of thrombin, the reaction mixture clots immediately upon being neutralised. (K. Laki and W. F. H. M. Mommaerts, *Nature*, 156, 664 (1945)). Thrombin acts catalytically, its role is to alter fibrinogen molecules to be able to unite through some kind of bonds. Redox-potential measurements show that during the clotting, reducing groups are being formed. Fibrinogen can be prepared from oxalated cattle plasma which clots on addition of ninhydrin, formol, various quinones, catechol plus potato oxidase, too. The action of these substances depends not only on pH but greatly depends on the fibrinogen concentration. If the fibrinogen solution is not concentrated enough, though all these substances react with fibrinogen, no clot is formed. It has been found that the formation of fibrin by the action of thrombin involved the same groups as the formation of the clot brought about by the action of formol or quinone, and that these groups cannot be SH groups since fibrinogen does not contain free SH groups. All these substances are known to react with amino-groups of proteins. At the optimal pH of their action neither formol nor quinone is expected to react with other groups. Clot obtained by the action of quinone is red and its formation very likely involves the same mechanism as described by E. Fischer and H. Shrader (*Ber.* 43, 525 (1910)) in the case of quinone and glycine when hydroquinone is formed during the reaction. The experiments with formol and quinone strongly suggest that the amino-groups of fibrinogen take

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part in the formation of fibrin, and that the role of thrombin is to form some groups on the fibrinogen molecules which can react with amino-groups like formol or quinone.

The procedure adopted to prepare thrombin for these experiments leads to preparations always containing copper and having usually a blue colour. The copper is bound to globulin. All these thrombin preparations colorize catechol and oxidize paraphenyldiamine. Though the oxidizing capacity is low compared with other oxidizing copper proteins, its oxidizing ability is in correlation with its clotting activity. The more active a preparation is as a clotting agent the more active it is as an oxidase.

MARTINI, E. and GUALTIEROTTI, T. (Milano). Two areas of the cerebral cortex which are apparently independent of the diencephalic center.

After the passage of interrupted current (280 H) through the diencephalon a condition similar to narcosis and the suspension of electrical activity in the different parts of the C.N.S. is observed.¹ When the same current is applied transversally to the spinal cord, the electrical activity of the caudal part stops, but only if the cord is still connected with the trunk of the brain.

After the destruction of a zone situated dorsally to the mammillary body it is no more possible to obtain the inhibition of the spontaneous medullary electrical activity by means of passage of square current.²

In the cerebellum analogous phenomena may be observed.³ An inhibition of the spontaneous cerebellar electrical activity may be obtained either by passage of a interrupted current through a determined zone of the cerebellar cortex, or by passage of the same current through the diencephalic-mesencephalic zone.

After a transversal section of the brain stem at level of the upper part of the pons, it is no more possible to inhibit the cerebellar electrical activity.

The application of the current to limited areas of the cerebral cortex, after the well-known manifestations of the convulsive activity, leads to a temporary inhibition of the electrical activity which may not be limited to the area invested by the current, but it extends to

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the rest of the cortex and to the other hemisphere.⁴ Nevertheless, in the cat, a zone corresponding to the frontal pole is not inhibited by the application of the current to the diencephalon. In this case wide and regular waves 10 H frequent are observed while the remaining of the cortex is electrically silent.¹ If the current is applied directly to this zone, the electrical activity is inhibited neither in this same zone, nor in the other cortical sectors. It looks as if this part of the cortex were independent from the diencephalic center of inhibition.

A cortical area with analogous characteristics has been shown in the occipital lobe of the dog involving apparently all the cortical visual area.

¹ Gualtierotti, T., Martini, E., and Marzorati, A., *Pflügers Archiv.* **246**, 351 (1942). ² Martini, E., Gualtierotti, T., and Marzorati, A., *Pflügers Archiv.* **246**, 585 (1943). ³ Martini, E., Gualtierotti, T., and Marzorati, A., *Boll. Soc. It. Biol. Sper.* **21** (1944). ⁴ Gualtierotti, T., Martini, E., and Marzorati, A., *Boll. Soc. It. Biol. Sper.* **21** (1944).

MITOLO, MICHELE (Bari, Italy). *d*- α -amino-acid oxidase in central nervous system.

Krebs (*Biochem. Journ.* **29**, 1620, 1951 (1935)) found that extracts of rat brain, tested on *dl*-alanine, do not contain measurable amounts of *d*-amino-acid oxidase. According to *Weil-Malherbe* (*Biochem. Journ.* **30**, 665 (1936)), an aqueous extract (but not slices) of brain (ox) is capable of oxidizing only one *d*-amino-acid, *d*(-)-glutamic acid, in presence of *d*-glutamic acid oxidase, different from the usual *d*-amino-acid oxidase.

I made a systematic investigation on *d*-amino-acid oxidase in central nervous system, as scarcely studied by *Krebs* on brain extracts of only one animal species (the rat). I took as a measure of oxidative deamination the ammonia production, using aqueous extracts of various sections of the central nervous system of different animal species; the extracts contain only *d*-, but not *l*-amino-acid oxidase (*Krebs*). As a substrate I used *dl*-alanine (*Merck*) or *d*-phenylalanine (*Merck*); arsenite was added to the system, as it, although does not inhibit the *l*- and *d*-amino-acid oxidase activity (*Krebs*, *Zeitschr. f. physiol. Chem.*, **218**, 157 (1933)), fixes ammonia (opposing to the synthesis of glutamine) and inhibits any further oxidation of the α -keto-acid.

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Portions of the central nervous system (300–500 mg.), taken immediately after killing (bleeding) the animal, were cut, washed, and minced in a centrifuge tube cooled with ice, in presence of quartz sand; the 'brei' was extracted with H_2O for 15–20 mins.; it was centrifuged and filtered. Two tests were prepared for each experiment: (a) 2 ml. extract+1 ml. arsenite (end-concentration 0.005 M)+1 ml. H_2O ; (b) 2 ml. extract+1 ml. arsenite+1 ml. amino-acid (end-concentration 0.0125 M), air at 38° with shaking from time to time. After 120 mins. 0.5 ml. of 10 % trichloroacetic acid was added in order to stop the reaction, and it was centrifuged; the liquid was made alkaline with 1.5 ml. saturated solution of barium hydroxide, and ammonia liberated (at $40-50^\circ$) was driven over by a CO_2 - and ammonia-free air current (by suction pump, for 15 mins.) into a known volume of $N/200 H_2SO_4$; the residual acidity was titrated iodometrically.

It was found that in some sections of the central nervous system (particularly brain gray matter) of toad, hen, guinea pig, rabbit, albino rat, dog, but especially cock, *d*-amino-acid oxidase is present (although not in high concentration as in liver or kidney); on the contrary the enzyme is missing in other sections of the central nervous system of the same animal species. *d*-amino-acid oxidase is not present in the central nervous system of green-bird, duck, and cat.

MOMMAERTS, W. F. H. M. (Beirut, Lebanon). Interactions between myosin and adenosin triphosphate.

Whereas it is increasingly believed that the primary energy yielding reaction in muscular activity is the splitting of adenosintriphosphate (ATP) by myosin—ATPase, it has been shown by the author and *Seraidarian*¹ that such a reaction cannot occur in contracting muscle at the required speed.

This result does not exclude the possibility that interactions between myosin and ATP, other than the splitting of the latter substance by the former, may occur and may be the cause of contraction. That ATP exerts physical effects upon myosin has been shown by *Szent-Györgyi*.²

The present paper gives an account of investigations on the nature

of such reactions, as an example of which the decrease of the viscosity of actomyosin solutions upon addition of ATP was selected.

It was found that this reaction is promoted by Mg- and counteracted by Ca-ions, whereas the activity of myosin-ATPase is affected by these ions in exactly the opposite sense.

It was further found that the effect of ATP can be imitated, be it under more special conditions, by substances related to ATP, but not enzymatically hydrolyzed by myosin.

Finally it was found that the effect of ATP takes place also when the enzymatical activity of the myosin has been destroyed.

From these experiments it is concluded that the physical changes induced in the myosin molecule by ATP have nothing to do with the hydrolysis of ATP by ATPase present in myosin preparations. It is supposed that the type of interactions between ATP and myosin investigated in this study form the primary event in muscular contraction.

Publications will be submitted to the *Journal of General Physiology*.

¹ Mommaerts, W. F. H. M., and Seraidarian, Krikor, *Journ. Gen. Physiol.*, 1947, May issue. ² Szent-Györgyi, A., *Acta Physiol. Scand.* 9, Suppl. 25 (1945).

PAES, EURICO (Lisbon). Chemical mediators as promoting agents of the origin of heart-rhythm.

Demoor and *Rijlant* demonstrated that extracts of nodal tissue (Keith-Flack nodes, Aschoff-Tawara centers, His' fasciculus, Purkinje's net), both aqueous and alcoholic, are capable of inducing regular rhythm in a heart fragment in which only rare twitchings, uneven intensity and frequency, have been observed. The 'Wild activity' of the myocardium is changed into 'Rhythmical automatism' under the influence of the nodal tissue.

The extracts of nodal tissue when heated (60° C.) lose their rhythm-inducing capacity.

Demoor and *Rijlant* interpret these facts in suggesting that in the extracts of nodal tissue, rhythm-inducing substances exist; *Haberlandt* states that in Batrachia the *Herzhormon* exists and *Zwaardemaker* suggests that the active substance of the heart rhythm is the *automatine*, brought about by the influence of potassium and other radioactive bodies, from the *automatinogène* existing

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throughout the body and conveyed by the blood into the heart, where it accumulates chiefly in the nodal tissue. However, *Bacq* and his co-workers are not in agreement with the aforementioned.

My experiments confirmed results obtained by *Demoor* and *Rijlant* and, furthermore, I observed the following facts:

1. The nodal extracts, 'inactivated' through heat (60° C.) may recover their rhythm-inducing properties, by subsequent addition of acetylcholine and adrenaline;

2. Acetylcholine and adrenaline, alone, i.e. without any 'inactivated' nodal extract), have no rhythmical power whatsoever;

I interpreted these facts concluding that, in the 'inactivated' extracts, a substance exists (not self-rhythm-inducing)—called by me *pre-rhythmia* and which, when under the action of acetylcholine and adrenaline, becomes a rhythm-inducing substance—called by me *rhythmia*.

On the other hand, and according to Loewi's theory of the chemical mediators, to-day universally accepted, the nerves as they are known, act through chemical substances which are released at their extremities, the pneumogastric releasing the *Vagusstoff*, identified presently as acetylcholine and the sympathetic nerves yielding adrenaline.

One may be led to think, after considering the above, that in the existing body, the *Vagusstoff* (acetylcholine) in the presence of the sympathetic substance (adrenaline), might act upon the *pre-rhythmia* (main characteristic substance of the nodal tissue), which might transform it into a rhythm-inducing substance. Moreover, the frequency of the heart-rhythm would depend at all times on the relation to the acetylcholine-adrenaline, in action.

Therefore, accepting this hypothesis as a conception of the genesis of the heart-rhythm, the reconciliation of the 'myogenist' and 'neurogenist' theories would result.

PARROT, J.-L., GABE, M., et HERRAULT, A. (Paris). Intoxication aiguë du Cobaye par administration gastrique d'histamine seule ou associée à la putrescine.

L'administration d'histamine au Cobaye par voie gastrique n'est suivie classiquement que de manifestations très discrètes (*Mellanby*,

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Koessler, et Hanke); ce fait est attribué à la destruction de l'histamine par l'histaminase intestinale. Cependant, certaines constatations incitent à attribuer un rôle pathogène à l'histamine intestinale (Akerblom, Legroux et collaborateurs). Nous avons pensé que l'histaminase intestinale pouvait dans ce cas être inhibée par une diamine, provenant, en même temps que l'histamine, de l'action décarboxylante de certains microbes. Nous avons donc étudié, sur le Cobaye, les effets de l'histamine introduite par sonde oesophagienne, à la suite de l'administration de putrescine par la même voie; il nous a fallu déterminer au préalable la toxicité des deux substances administrées isolément:

Toxicité du dichlorhydrate d'histamine par voie gastrique

<i>Dose en mg./kg.</i>	<i>Nombre d'animaux</i>	<i>Nombre de morts</i>	<i>Pourcentage de morts</i>
100	10	1	10
200	10	3	30
300	10	6	60
400	10	8	80

Toxicité du dichlorhydrate de putrescine par voie gastrique

<i>Dose en mg./kg.</i>	<i>Nombre d'animaux</i>	<i>Nombre de morts</i>	<i>Pourcentage de morts</i>
800	4	0	0
1000	6	0	0
1200	10	6	60
1500	6	6	100

Toxicité combinée de l'histamine et de la putrescine

<i>Dose en mg./kg. Histamine</i>	<i>* Putrescine</i>	<i>Nombre d'animaux</i>	<i>Nombre de morts</i>	<i>Pourcentage de morts</i>
15	75	8	0	0
20	100	6	0	0
25	125	10	0	0
30	150	10	6	60
35	175	10	9	90

Les animaux ayant reçu l'histamine seule à dose suffisamment

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élevée meurent en 3-4 heures. L'examen histologique montre une congestion intense des viscères, des érosions saignantes de la muqueuse gastrique, souvent des perforations. Chez les animaux intoxiqués par la putrescine seule la mort est plus tardive; à l'examen histologique on constate une stéatose massive du foie et des lésions d'alvéolite aiguë du poumon, mais jamais d'érosion gastrique ni de congestion viscérale. Administrée après putrescine, l'histamine détermine, dans les mêmes délais, des lésions identiques à celles qu'elle provoque à des doses 5 ou 6 fois plus fortes lorsqu'elle est seule.

PATTERSON, T. L., KAULBERSZ, J., SANDWEISS, D. J., and SALTZSTEIN, H. C. (Detroit, Mich.). Gastric secretory effects of urogastrone and enterogastrone from hypophysectomized dogs.

In a series of experiments on partially endocrinectomized animals to determine the possible origin and influence of urogastrone, a gastric secretory depressant obtained from urine (*Science*, 102, 530 (1945); *Proc. Can. Physiol. Soc.* (1945), page 15; *Can. Med. Assoc. Journ.* 54, 69 (1946); *Federation Proceedings*, 5, No. 1, 54 (1946); *ibid.* 6, No. 1, 140 (1947)), the question arose as to the effects of urogastrone and enterogastrone prepared from hypophysectomized dogs on gastric secretion.

The hypophyses were removed from six normal female dogs by the transtemporal method which was substituted for the transbuccal procedure employed in our previous studies. After collecting sufficient urine for the preparation of urogastrone, the animals were sacrificed and enterogastrone was prepared from the mucosa of the small intestine. Both urogastrone and enterogastrone were then tested separately by the intravenous route for their gastric secretory depressant effects on Heidenhain pouch and gastric fistula dogs using histamine diphosphate in doses of 0.5 to 1 mg. as the gastric secretory stimulant.

The extract prepared from the small intestine (enterogastrone) demonstrated the typical inhibition of gastric secretion in nearly all of the studies, whereas the extract made from the urine of the same animals (urogastrone) stimulated gastric secretion in 60 % of the

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experiments and inhibited the secretion in only 27 %. In the remaining 13 % of the studies there was no significant change.

This increase in the gastric secretion which occurred in the majority of cases resulting from the administration of urogastrone obtained from hypophysectomized animals may suggest that with a disturbance in the pituitary gland, factors come into greater play that augment the action of gastric secretory stimulants, thus contributing to peptic ulcer formation.

REISS, M., and REES, D. S. (Bristol). **Brain metabolism and pituitary.**

The hexokinase activity of brain suspensions of hypophysectomized rats is about 25% higher than that of brain suspensions of normal control rats. After adrenalectomy, too, the hexokinase activity is considerably increased.

The anaerobic glycolysis of tissue slices of the grey substance is increased by 25-40 % after hypophysectomy and can be reduced again by treatment with corticotrophic hormone. The oxygen consumption of brain slices is, in contrast to other organs, only considerably decreased after hypophysectomy.

The vitamin 'C' content of the brain is decreased by 30-70 % after hypophysectomy.

SAWAYA, PAULO (São Paulo, Brazil). **Metabolism of the Lung-fish, *Lepidosiren paradoxa* and the Limbless-amphibian, *Typhlonectes compressicauda*.**

Active air-breathing fish (*Dipnoi-Lepidosiren paradoxa*, 86 grs. weight) and Limbless-amphibian (*Gymnophiona-Typhlonectes compressicauda*, 138 and 64 grs.) were tested in a new respirometer to determine the respiratory metabolism. Both animals live in the neotropical freshwaters where they are occasionally or regularly exposed to oxygen deficiency. Their organs for respiration in water are poor structures; in *L. paradoxa* the gills are reduced and seem inadequate to respiration, and *T. compressicauda* has no special organ for aquatic respiration, but the skin. Notwithstanding, both animals are unable to live exclusively in water or air. The animals were kept without food, and during the period of observation

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(2-8 hours) they were confined to the metabolism chamber in 750 ml. of tap-water. One or two hours later while they lay quietly on the bottom, the chamber was tightly closed. Sometimes the animals moved only to breathe. Samples of water and air were withdrawn before and after the experiments; water by syphoning and air by one tube connecting the chamber with the Haldane analyzer. The results indicate that the fish and the amphibian use very little of the oxygen dissolved in water (*L.p.* 0.100-0.475 and *T.c.* 0.044-1.062 ml. per hour). Air is the principal source of oxygen supply, the fish consuming 5.099-6.175 and the amphibian 3.300-10.950 ml. per hour. More CO_2 is released in water than in air by the *Typhlonectes* (1.350-4.050 in water and 0.950-3.750 ml./h. in air) and the contrary occurs with the fish (0.100-1.220 in water and 0.700-1.950 ml./h. in air). These results confirm the effectiveness of the amphibian skin for CO_2 excretion. R.Q. of the fish remains between 0.1 and 0.3, and that of amphibian between 0.4 and 0.8. Mineral contents of water were determined before and after each experiment. In both cases only increasing of Ca is significant (12 %). It is interesting to observe that the traces of iron determined in tap-water (0.31 mg. per liter) disappeared very quickly after the animals were placed in it. The results of several determinations indicate: (1) *L. paradoxa* and *T. compressicauda* depend on oxygen supply of water and air; (2) Both have chiefly aerial respiration, but are unable to live indefinitely in air; (3) In the case of *Typhlonectes* the skin is the principal organ for CO_2 excretion; (4) Absorption of oxygen dissolved in water corresponds to 1-8 % (case of the fish) and 1-6 % (case of the Amphibian) of the absorption of the gas taken from the air.

TANKÓ, B. (Debrecen, Hungary). Phosphorylation in muscle. The components of the phosphorylating system glycogen+inorganic phosphate+pigeon muscle were studied. The phosphorylating activity of fresh muscle mince is fully retained in the muscle powder prepared from it with alcohol and ether. The phosphorylation of the washed powder can be restored either (a) by adding boiled extract of powder or (b) by adding Mg., cozymase, and adenylic acid (AP) yet there is the pronounced difference that the esterified

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mg. P (in 2.5 ml. total volume 0.25 gm. powder, washed, incubation 1 hour, room temperature) is decreased, e.g. from 4.4 to 3.6 in (a), but from 4.3 to 1.3 in (b) on addition of m./50 NaF.

In order to explain this difference, the possible factors the boiled extract might contain besides cozymase, Mg. and AP were investigated. As shown by earlier experiments (Tankó, *Ber. Ges. Physiol.* 131, 239 (1942); *ibid.* 134, 185 (1943), 'heat stable' enzyme proteins were not involved nor were simple inorganic ions. The resistance to NaF was not attained by addition of ATP in amounts equivalent to the AP found to be optimal in (b) without NaF. Oxaloacetate or pyruvate added together with fructosediphosphate yielded a phosphorylation resistant to NaF like system (a), none of these compounds were found in the boiled extract however or at least by far not in such amounts that proved to be necessary in model experiments.

Further investigations revealed that P-creatine takes no part in system (a). Increasing the ATP to 400 % over the equivalent AP sufficient in (b) without NaF, however, led to a phosphorylation resistant to NaF. The problem was approached from the preparative side too: working up the boiled extract the labile P—which according to Kiessling's method appeared to be *Cori-ester*—was found and identified as ATP in the sparingly soluble Ba-salt. It may be pointed out that Lohmann's observations seemed to exclude in advance the occurrence of ATP in the boiled extract.

To see if there are any other factors included in (a) the cozymase Mg., AP and ATP content of the boiled extract was carefully determined. These components employed in the same amounts in model experiments qualitatively and almost quantitatively explained the behaviour of (a). The sensitiveness to NaF of the system without ATP may so be attributed to the known fact that the reaction $ADP \rightleftharpoons ATP$ needs no Mg whilst the reaction $AP \rightleftharpoons ADP$ does and so in concentrations of NaF employed here only the former works. This was corroborated by substituting ADP for ATP with the same success. Yet the findings with oxaloacetate or pyruvate and fructosediphosphate (see above), seem to await explanation.

WU HSIEN, and CHOU CHI-YUAN (Peiping). Relative rates of denaturation of egg albumin by aliphatic alcohols.

Under constant temperature (25° C.), pH (10.5) and ionic strength (0.1-M borate buffer), the rates of denaturation of egg albumin by methyl, ethyl, n-propyl and n-butyl alcohols increase at first slowly with increasing alcohol concentration, then sharply with further increase. The turning points for the four alcohols are approximately at 33, 22, 11, and 5.5 volume % respectively.

Measured by the molal concentration of alcohol which will bring about 50 % denaturation of albumin (0.5 %) in one hour under the above-mentioned conditions, the relative denaturing powers of methyl, ethyl, n-propyl and n-butyl alcohols are approximately in the ratio of 1, 2, 6, and 15.

The initial rate of denaturation of albumin (0.5 %) by ethyl alcohol (26 %) at 30° C. is 20 times that at 20° C. This high temperature coefficient indicates that the mechanism of denaturation of albumin by alcohols is different from that of ordinary chemical reactions in solution.

The increase in denaturing power of aliphatic alcohols with length of C-chain suggests that the volume of the alcohol molecule is an important factor in denaturation. According to the theory advanced by one of us (*Chin. J. Physiol.* 5, 321 (1931)), denaturation is disorganization of the natural protein molecule. The alcohol molecule, by virtue of its hydroxyl group, is attracted by the polar groups, and penetrates between the folds of the albumin molecule. This penetration causes, by disruption of the secondary valence bonds, disorganization of the albumin molecule, and the larger the size of the alcohol molecule the greater is the disruptive effect.

SOMOGYI, J. C. (Wolhusen, Switzerland). On plant-substances inhibiting the oxidation of ascorbic acid.

According to previous publications,^{1, 2, 3} the oxidation of ascorbic acid in unfiltrated orange- or lemon-juice is slower than in filtrated. We suggested that the filter-rest of plant juice contains substances, which inhibit the oxidation of ascorbic acid. Also our own observa-

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tions^{4,5} about the loss of ascorbic acid during the drying process of different fruits and vegetables point to the existence of such plant substances.

At first a method was worked out which made it possible to determine the activity of these plant-substances with a rather good accuracy. We prepared pulverized concentrates—called substance B'—from the filter-press of different plants and their activity was defined.

Substance B' of lemons is the most active of all plant substances which were investigated. In a concentration of 6% it completely inhibits—under the described experimental conditions—the oxidation of ascorbic acid during 90 minutes.

In order to define the contents of the protective substances in different plants these were expressed in units. One unit is one-hundredth part of this amount of plant-substance, which completely inhibits for 60 minutes the oxidation of an ascorbic acid solution of 15 mg.% after addition of ascorbic-oxidase (extract of white cabbage) of defined activity at pH 6 and maintained at 39° C.

Hitherto are determined in thirty plants the contents of protective substances and simultaneously the total capacity of oxidation. That was determined by the speed of the oxidation of ascorbic acid, i.e. we defined the amount of vitamin C, which was oxidized in a minute.

The loss of vitamin C during the drying process can only be explained in regard to the contents of protective substance as well as to the oxidizing capacity of the same plants. These protective substances have in any case a primary importance for the loss of ascorbic acid during the drying process. It seems to be possible to express the amount of protective substance and the total oxidizing capacity by one single factor and so characterize the value of the plant as a vitamin C carrier.

After we determined the contents of the protective substances of the oxydases and of vitamin C as well as the loss of ascorbic acid during the drying in the different plants, it was interesting to investigate also the change of all these factors during the ripening-, storage- and cooking-processes. It was found that the contents of ascorbic acid and of substance B' increased in tomatoes during the ripening-process and at the same time diminished the oxidizing capacity.

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Therefore the loss of ascorbic acid also diminishes during drying process.

The importance of these protective substances for the oxidation of ascorbic acid is discussed in detail.

- ¹ Vitte and Coustou, *Bull. Trav. Soc. Pharmac. (Bordeaux)* **80**, 114 (1942).
² Strohecker, R. and Buchholz, E., *Z. Unters. Lebensm.* **83**, 122 (1942).
³ Somogyi, I. C., *Helv. Physiol. Acta.* **2**, 269 (1944). ⁴ Somogyi, J. C. *Helv. Physiol. Acta.* **1**, C 50 (1943). ⁵ *Zsch. f. Vitaminf.* **16**, 134 (1945).

COMENGE, M. (Madrid). **On the metabolism of Bombyx Mori, L.**

By means of the parallel analysis of the leaf of *Morus alba* and of the silkworm at the end of each instar, taking into account the residual leaf and the excrements, we have succeeded in establishing the metabolism of proteins, carbohydrates and fats in all the instars and the pupa and imago, both before and after copulation. These data have enabled us to reach the following conclusions:

1. The voracity of the larva ($\frac{\text{leaf ingested}}{\text{weight of larva}} = V$) is very great on hatching ($V = 8$); becomes progressively smaller up to the fourth instar ($V = 1.8$); and increases again from this time until the spinning period, while still remaining lower than at hatching ($V = 3.9$).
2. The curve representing the weight of the larva is approximately logarithmic in respect of the time.
3. The metabolism of water and that of all dry material are complementary, always very intense, although from the second instar onwards a slight diminution in weight is noticeable, which becomes more evident during the period from the fourth to the fifth instars. The weight curve falls from this time and continues its descent until the death of the insect.
4. In the period of pupation the metabolism of dry matter provoked by metamorphosis is in accord with the pattern of economy during the fast.
5. The transformation of the pupa into a male imago requires the metabolizing of a greater quantity of dry matter than the pupa-female imago transformation.
6. Metabolism of dry matter decreases in the female and increases in the male during copulation.

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7. The elimination of water in the act of copulation is extraordinary in the male (5.9 gr. per 1,000 larvae).

8. Carbohydrates are the energy-producing foods most immediately utilized by the silkworm. *Bombyx mori*, L. digests cellulose.

9. The larva of *Bombyx mori*, L. synthesizes fats from the fourth instar onwards, forming the energy reserve of the pupa.

10. The intensive assimilation of protein during the first four instars (1st instar = 80.3%; 2nd = 71.8%; 3rd = 65.7%; 4th = 66.1%) changes into an active metabolism of protein at the fifth instar, with a notable decrease in protein assimilation (7%).

11. The fourth instar marks a coincidence of minima in the centesimal composition of the silkworm. For carbohydrates and ash the minimum occurs in the fifth instar.

12. The composition of the mulberry leaf is not correlated with that of the silkworm which feeds exclusively upon it.

SANTOS RUIZ, A., and LUCAS GALLEGO, J. (Madrid). **Observations on the production of specific 'proteinases' in the organism.**

The Abderhalden reaction of defensive 'proteinases' permits the diagnosis and location of cancer, as well as of its recurrence and metastasis. Its importance in proving the cure of cancer is evident. Precision in the diagnosis of cancer, anatomically and pathologically, can be achieved in the initial stage.

The existence of other tumoral and infectious diseases (e.g. lymphogranuloma) can be diagnosed by the specific 'proteinase' technique.

Experiments carried out on rabbits injected with diphtheria toxin and 'anatoxin' confirm the appearance of specific defensive 'proteinases'. Tests with live diphtheria bacilli demonstrate the production of defensive enzymes which disintegrate the substrata of bacillus and toxin; those with dead diphtheria bacilli act only on the bacillus substratum; and those with diphtheria toxin only hydrolyse the toxin substratum. The secretion of defensive enzymes is maintained until the cure of the condition, notwithstanding treatment or vaccination with 'anatoxin'. Cases in which the intensity of the reaction is low are those which follow the gravest course, since the defensive capacity

of the organism is diminished. The reverse happens when the reaction is intense. The production of specific enzymes is more rapid for the proteins of bacilli than for those of toxin.

Suprarenal hypofunction induced by the experimental extirpation of one or both suprarenal capsules in the cat does not give rise to the formation of specific defensive enzymes. Suprarenal hypofunction caused by the trituration *in situ* of one or both suprarenal capsules, the animal retaining remnants of destroyed chromaffinic tissue, causes the production of defensive enzymes in the urine. Suprarenal hyperfunction produced experimentally by parenteral administration of cortical hormone or of adrenalin does not bring about the formation of defensive enzymes in the cat. Cortical hormones administered parenterally to animals which have given a positive result after bisuprarenotomy with trituration *in situ* favour the negativity of the Abderhalden reaction. In animals deprived of the suprarenal capsules the administration of foreign albumens (e.g. milk) causes the production of defensive enzymes, but of non-specific characteristics. Parenteral administration of albumens obtained from the suprarenal capsules of animals of the same or different species gives rise to the appearance of defensive enzymes. The technique of demonstrating the presence of defensive enzymes in the urine does not allow the diagnosis, in the cat, of the hormonal alteration of the suprarenal capsules.

SANTOS RUIZ, A., and LUCAS GALLEG0, J. (Madrid). Some results relative to physiological and pathological variations in the glutathione level in blood.

The glutathione in blood has been measured by the *Binet-Weller* technique modified by A. Santos Ruiz and M. Rollant.

The variations in glutathionemia in experimental anoxia, cancer, lymphogranuloma, and other hyperplastic, parasitic, and inflammatory conditions, as well as in tuberculosis and syphilis, have been studied and the following conclusions reached.

Animals submitted to the action of coal gas show a change in which the G-SH increases, GS-SG falls, and GST remains invariable. In animals poisoned with CO₂, the G-SH showed no constancy in its variations, while the GS-SG and the total glutathione (GT)

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increased in the majority of cases. At the end of the coma the figures returned to normal. In an atmosphere of nitrogen there is, at the peak of asphyxiation, a rise in the total glutathione and the GS-SG, with a less marked increase in G-SH.

In the total blood of untreated cancer patients the GS-SG and GT decrease and G-SH increases. In some cases the GS-SG is nil. There appear to exist an inverse relation between the decrease of GT and GS-SG and the gravity of prognosis, and a direct relation with the increase of G-SH. In the total blood of cancer patients treated with favourable results GT and GS-SG increase and G-SH decreases. Radiotherapy raises the figure for GS-SG in 100% of cases and for GT in 63%. No modifications of the GT and its fractions in relation to the variety of the tissue irradiated were apparent. The quotient of the difference between the figures for G-SH, before and after treatment, and the difference between the corresponding figures for GS-SG we call the glutathione factor. Quotients above 1.50 imply grave prognosis and lower figures favourable prognosis.

Sufferers from lymphogranulomatosis and similar conditions give analogous conclusions.

In pulmonary tuberculosis the GT is diminished in 80% of cases, GS-SG in 56.6%, and G-SH in 60%. An increase in GT and GS-SG occurs in serious forms. When pleurisy is present the figures are lower than those observed in tuberculosis without pleurisy; similarly G-SH decreases in articular and peritoneal inflammatory conditions.

In syphilitics the GT falls in 8.3% of cases; the oxidised form in 20%; and the reduced form in 96%. The diminution of GT is in direct ratio to the intensity of the serological reaction. The glutathione and its fractions, particularly the oxidised form, decrease in serum.

SOLS, A., and PONZ, F. (Barcelona). A new method for the study of intestinal absorption.

An original method for the study of intestinal absorption *in vivo* is presented. Technically it consists in connecting a portion of intestine *in situ* to a system for the conduction of liquids by means of

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special tubes applied to its extremes. This technique, when the abdominal cavity is sealed off, permits the controlled filling and washing out of the isolated loop as many times as may be required, or the continuous flow along it of the solution to be absorbed.

Physiologically the method rests on the fact, discovered by the authors, that an animal (rat or dog) not submitted to previous fasting absorbs, under constant conditions, approximately equal quantities of a given sugar per unit of time. This allows one to measure differences in the rate of absorption of different sugars placed in turn in the loop of intestine utilized; or to study, still by means of successive tests with the same loop, the influence of any substance or of a change in the experimental conditions on the absorption of a given sugar.

This constancy in the rate of absorption lasts for three hours at least in rats anaesthetized with urethane, allowing four or five successive experiments of 30 minutes each to be carried out.

The method is very simple in operation and assures the recovery of the substance not absorbed. Conclusions can in this way be reached with a great economy in animals, since the absorptions are compared in the same intestinal loop of the same animal.

If the solution to be absorbed is made to flow continuously through the loop one can investigate the effect of the continual renewal of the intestinal contents which the carrying off of secreted products involves.

The authors present the results obtained in rats with series of selective and non-selective sugars.

T. CUNLIFFE BARNES (Philadelphia, Pa.). Electrical phase-boundary potential of acetylcholine.

A portable one-channel electroencephalograph records signals produced by the addition of acetylcholine to an oil-saline interface. 3 c.c. of guaiacol (or other oil having OH groups for conductivity) is placed in a cup forming the end of a U-tube of saline immersed in 200 c.c. of saline to test the electrogenic action of substances present in nerve (Beutner and Barnes, *Science*, 94, 211, 1941). The aqueous phase on each side of the oil layer (model of the lipoid surface of nerve) is connected with input circuit of a Garceau electroencephalo-

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graph having grids of a pair of push-pull triodes going directly to the electrodes. 20 megohm shunts are placed in the grid circuits. The grids are near floating potential. The apparatus runs on house current and the inkless writing stylus records by electrical means on dry tape.

0.2 c.c. of saline is added near the oil surface in the 200 c.c. beaker without effect (some oil-cells give a positive deflection much smaller than the negative wave of acetylcholine in saline). 0.2 c.c. of 0.01 M KCl in saline has little or no effect, whilst 0.2 c.c. of 0.01 M acetylcholine in saline produces a negative wave of several millivolts (usually followed by a positive wave forming curves resembling classical diphasic variation in nerve). The exact shape of the wave cannot be demonstrated by a direct-writing oscillograph but it is significant that acetylcholine produces a signal at a molarity where all other nerve substances tested give no deflection. Disturbance of the oil surface distorts the acetylcholine wave but a similar disturbance produced by addition of the saline control has little effect unless the layer is broken. Records taken without an amplifier (electrocardiograph) will be exhibited showing that the down-stroke of the spike is not determined by the time-constant of the electroencephalograph.

The demonstration suggests that (1) spike potentials can be produced by a phase-boundary mechanism at an oil-saline interface; (2) there is no need to postulate the existence of an imaginary Bernstein membrane; (3) inorganic ions like potassium have very feeble electrogenic action at an oil-saline interface resembling the nerve fiber; (4) lipid-soluble organic substances like acetylcholine, thiamine and sympathin probably produce the action currents in nerve; (5) choline esterase is not essential for impulse formation; (6) the curare-like action of prostigmine can be duplicated by introducing the drug into the oil prior to the tests described above.

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